FEBRUARY 1955
VOL. XI NO. 2

Circulation

e JOURNAL of the AMERICAN HEART ASSOCIATION

OSTON UNIVERSITY
EGE F LIBERAL ARTS
LIBRARY

Published by Grune & Stratton, Inc.

To help the kidneys

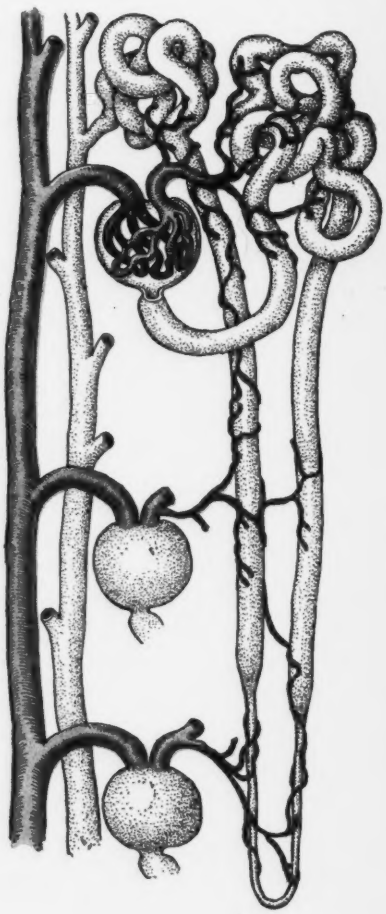
rid the body of excess fluid

SALYRGAN®-THEOPHYLLINE

Dependable mercurial-xanthine diuretic

—prevents reabsorption of water and sodium by the renal tubules.

Elimination of sodium as well as water decreases the body's capacity to retain fluid.



Parenteral administration (intramuscularly or intravenously) of Salyrgan-Theophylline dependably reduces edema and ascites in cardiovascular failure, nephrosis and hepatic cirrhosis.

Oral administration of Salyrgan-Theophylline tablets has become an established routine for interim diuresis — between parenteral administration — and for milder cases of edema and ascites. Patient response regulates the oral dosage.

SUPPLIED:

Ampuls of 1 cc. and 2 cc.—boxes of 10, 25 and 100.

Tablets —bottles of 100, 500 and 1000.

Another useful aid:

NEOCURTASAL®

Salt without Sodium

2 oz. shakers • 8 oz. bottles

Winthrop-Stearns INC.

NEW YORK 18, N. Y. WINDSOR, ONT.

Salyrgan (brand of mersalyl) and Neocurtasal, trademarks reg. U. S. Pat. Off.

Circulation
The Journal of the American Heart Association

FEBRUARY 1955
VOL. XI NO. 2

The Circulatory Effects of Reserpine

By E. G. McQueen, M.B., M.R.C.P., A. E. Doyle, M.D., M.R.C.P., and F. H. Smirk, M.D., F.R.C.P.

The effects of large doses of reserpine have been compared in hypertensive and normotensive patients. The falls of blood pressure are larger in the hypertensives than in the normotensives. In normotensive animals small falls of blood pressure occur. Evidence is presented which suggests that the fall of blood pressure in animals is in part mediated through the sympathetic nervous system. There seems also to be a direct vascular action in animals. In man, evidence is presented which suggests that part at least of the hypotensive action is mediated through the sympathetic nervous system.

THE pharmacology of extracts of *Rauwolfia serpentina* has been studied by Chopra and co-workers,[1] Ray and associates,[2] and Dasgupta and colleagues.[3] Chopra and associates[1] reported that the alkaloid with which they were working had a marked hypotensive effect which was in part due to depression of central nervous mechanisms, since it was less marked in decerebrate animals; it appeared also to result in part from a direct inhibitory effect on the musculature of the blood vessels. They also demonstrated a fall in the output of the isolated heart. Most subsequent work has suggested that the hypotensive effect of Rauwolfia alkaloids is mediated solely via central nervous mechanisms.

A new alkaloid, now named reserpine, was isolated by Müller and co-workers[4] and pharmacologic studies on the action of this alkaloid have been published by Bein and colleagues,[5, 6] and Trapold and associates.[7] These workers reported that reserpine produced its hypotensive effect through the central nervous system, and they emphasized particularly its capacity to inhibit reflex pressor responses.

From the Department of Medicine, Otago University Medical School, Dunedin, New Zealand.

This work was supported in part by the Life Insurance Medical Research Fund of Australia and New Zealand and in part by the Medical Research Council of New Zealand.

Since the falls of blood pressure obtained in normotensive animals with this drug are often inconspicuous, while the falls of blood pressure in hypertensive patients are occasionally very large, it was decided to compare the effects of reserpine on the blood pressure in human subjects with hypertension and in those with normal blood pressures. The action of the drug in laboratory animals has also been studied and evidence as to a mode of action is presented.

Hypotensive Action of Reserpine

(a) *In Human Hypertensive Subjects*

The acute effects of large doses of reserpine have been studied in 33 hypertensive patients. The type of hypertension varied from grade I to IV.[8] The doses given were from 2 to 3 mg. three times daily by mouth.

The extent of the hypotensive response differed widely in individual subjects (table 1). In some, falls of blood pressure were obtained which were within the range commonly noted with the administration of placebos.[9] In others very large falls of blood pressure occurred, the blood pressure occasionally reaching normal levels. Although large falls of blood pressure occurred more frequently in those with low basal blood pressures, the lowest pressures recorded after reserpine were usually lower than the basal blood pressure; moreover, some

TABLE 1.—*Effects of Large Doses of Reserpine in Hypertensive Patients*

No.	Daily dose reserpine (mg.)	Casual B. P. before reserpine	Casual B. P. after reserpine	Fall in B. P.
114	8	204/108	200/110	4/2
183	5	208/120	185/108	23/12
194	5	260/160	180/105	80/55
269	9	230/142	200/118	30/24
277	9	198/118	188/100	10/10
288	4	204/130	160/100	44/30
293	9	232/124	148/90	84/34
363	4	170/110	130/80	40/30
376	9	214/118	210/118	4/0
729	9	238/118	210/110	28/8
733	3	192/118	152/88	40/30
750	9	224/118	160/100	64/18
755	9	198/126	150/90	48/36
765	5	162/110	140/88	22/22
766	3	214/138	115/62	99/76
767	9	228/130	190/118	38/12
768	9	206/128	130/75	76/53
770	6	196/124	150/98	46/26
771	9	254/140	140/82	114/58
772	9	230/140	135/90	95/50
778	4	204/138	190/120	14/18
902	9	192/132	160/100	32/32
903	4	200/110	180/100	20/10
904	4	180/130	160/120	20/10
908	4	190/110	120/80	70/30
911	9	180/120	140/100	40/20
912	9	224/140	160/110	64/30
919	9	250/130	224/126	26/4
923	9	260/140	220/120	20/20
927	6	210/140	160/110	50/30
930	3	180/110	160/90	20/20
931	4	190/100	150/90	40/20
932	9	220/120	210/105	10/15

patients with malignant hypertension and some with high basal blood pressures had large falls of blood pressure with reserpine. Postural hypotension did not occur, the blood pressure being unaltered over periods of up to 15 minutes at a 60 degree tilt with the feet down.

The effect of reserpine on the level to which hexamethonium reduces the blood pressure was observed in five cases. In these hexamethonium was given intravenously in divided doses with the patient recumbent until two successive doses failed to lower the blood pressure further. The test was repeated after large doses of reserpine had been given. The results are given in table 2. It will be seen that in all

TABLE 2.—*Effect of Reserpine on Minimum Blood Pressure after Intravenous Hexamethonium*

No.	Before Reserpine			After Reserpine		
	Casual B. P.	Min. B.P. after hexamethonium	Fall with hexamethonium	Casual B.P.	Min. B.P. after hexamethonium	Fall with hexamethonium
912	224/140	156/96	68/44	160/110	136/92	24/18
902	192/132	155/100	37/32	160/100	124/80	26/20
923	300/160	176/100	124/50	220/120	156/100	64/20
931	190/100	140/80	50/20	150/90	135/75	15/15
932	220/120	145/85	75/35	210/105	140/80	70/25

cases the blood pressure could be reduced to a lower level by hexamethonium after the hypotensive effect of reserpine had become manifest. The falls of blood pressure produced by hexamethonium were smaller, an observation which suggests that part of the neurogenically maintained constriction had been abolished by the action of reserpine.

The blood pressure did not usually begin to fall for three to five hours after a dose of reserpine had been taken by mouth. When the drug was taken thrice daily, the lowest blood pressure was usually noted within 48 hours. The fall of blood pressure with these large doses was preceded by marked blushing of the face and marked conjunctival injection. Miosis and bradycardia were also noted. Some patients complained of diarrhea and in some there was marked shivering and tremor. A few complained of mental depression, nightmares and insomnia, although extreme drowsiness was more commonly noted. With smaller doses such as 0.25 to 1.5 mg. daily, the severe side effects described above do not often occur. With such doses the hypotensive action may not become maximal for about 14 days. Conspicuous falls of blood pressure occur in only about one-fourth of patients tested,[10] particularly those with labile blood pressures.

(b) *In Normotensive Subjects*

The hypotensive effects of reserpine have been examined in 12 subjects with normal blood pressures. The results are presented in table 3. It is evident that the blood pressure falls are much smaller in normotensive subjects than

TABLE 3.—*Effects of Large Doses of Reserpine in Normotensive Subjects*

No.	Daily dose reserpine (mg.)	Casual B.P. before reserpine	Casual B.P. after reserpine	Fall in B.P.
1	9	128/80	90/52	38/28
2	9	140/90	130/80	10/10
3	9	145/90	108/68	37/22
4	9	145/90	120/75	22/15
5	9	125/80	112/70	13/10
6	9	135/80	90/60	45/20
7	9	140/70	124/66	16/6
8	9	145/90	140/80	5/10
9	9	135/70	106/60	30/10
10	9	140/90	106/60	34/30
11	9	110/75	98/60	12/15
12	9	140/80	124/76	16/4

in hypertensive subjects if the average fall is considered. By contrast the associated symptoms did not differ to any appreciable degree in the normotensive group from those noted in the hypertensives; facial flushing, conjunctival injection, miosis, nasal congestion, shivering, diarrhea and sleepiness were noted by most patients.

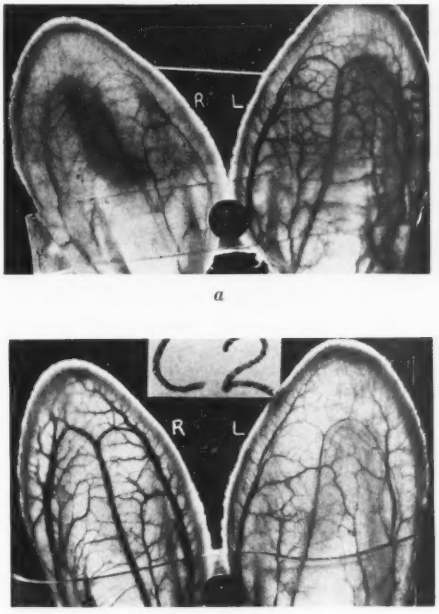
EFFECTS OF RESERPINE ON NORMOTENSIVE ANIMALS

(a) *Cutaneous Vasodilatation*

In rabbits, as in man, reserpine produces cutaneous vasodilatation which can be seen in the vessels of the ear. This action was investigated in the following experiment.

Method

In 18 rabbits the cervical sympathetic trunk on the left side was removed, together with the superior cervical ganglion and as much of the stellate ganglion as could be reached by the anterior approach. After a week had elapsed the animals were placed in boxes over a tray of ice with their heads exposed, and the ears cooled moderately from behind by an electric fan. Both white and gray rabbits were used. Because of the size of the ears and their vessels, the former provided the more striking results. One mg. per kilogram of reserpine was administered intraperitoneally. The size of the central artery of each ear was measured before and after the injection. The measurement was made at corresponding points on the artery using an arbitrary scale inserted into the eye-piece of a low-power dissecting microscope. In control experiments in 13 rabbits similar measurements were made before and after the intraperitoneal injection of 100 mg. of sodium nitrite.



a

b

FIG. 1. Rabbit ears (*a*) before reserpine, (*b*) after reserpine. The sympathectomized ear is on the right of the photograph.

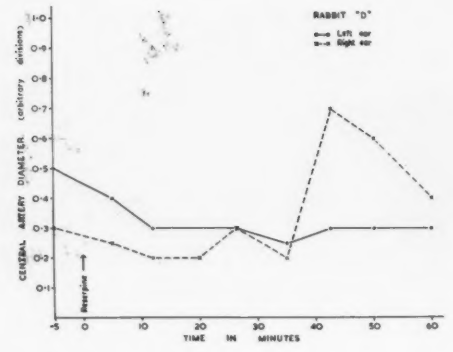
Results

Figure 1 shows the ear vessels of a white rabbit in which the cervical sympathetic chain on the left side had been avulsed one week before. In *a* the rabbit is seen before and in *b* one hour after 1.0 mg. of reserpine (rabbit weighed 1 Kg.).

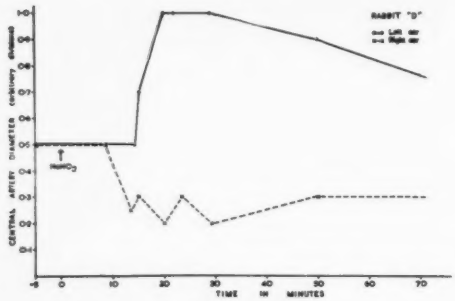
Table 4 shows the results of the measurements. Maximal dilatation of the innervated ear was apparent with reserpine at about three-quarters of an hour to an hour. With nitrite the maximum effect was evident after about 10

TABLE 4.—*Effect of Reserpine and Sodium Nitrite on Central Artery of Rabbit's Ear*

		Artery dilates	No change	Artery contracts
Reserpine (18 animals)	Innervated ear	15	3	0
	Denervated ear	0	11	7
Sodium nitrite (13 animals)	Innervated ear	7	3	3
	Denervated ear	6	5	2



a



b

FIG. 2. The alterations in caliber of the ear vessels of a white rabbit (*a*) after reserpine, (*b*) after sodium nitrite. Ordinates are in arbitrary divisions (see text); abscissa, time in minutes.

minutes. Serial measurements in a white rabbit are shown in figure 2.

It will be seen that after sodium nitrite there was no consistent tendency for one or other ear to be especially affected, as might be expected from an agent that acts directly on the vessels. By contrast, reserpine usually produced dilatation in the innervated ear, but either no change or even constriction in the denervated ear. These experiments suggest, therefore, that the cutaneous vasodilating action of reserpine in conscious rabbits is mediated mainly by the nervous system.

(b) *Effects on Blood Pressure*

In Rabbits. The blood pressure was measured by the ear method[11] in a number of conscious rabbits before and after reserpine. Although in some there was a fall in blood pressure at about the time of the maximal cutaneous

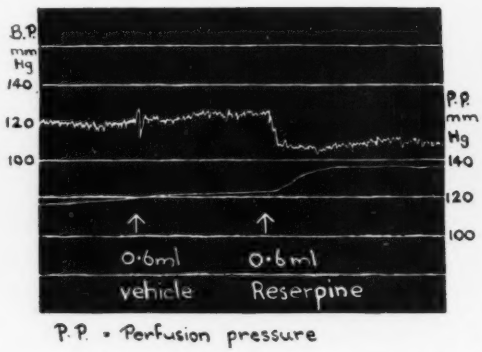


FIG. 3. Gray rabbit, 1.5 Kg. Upper record, systemic blood pressure recorded via carotid artery. Manometer scale shown on left is mm. Hg. Lower record perfusion pressure in isolated innervated hind limb. Manometer scale on right. At arrows injection made into a cannula situated in an external jugular vein. Vehicle is that supplied by Ciba Ltd. for use as a solvent for reserpine. Six-tenths ml. reserpine (in solvent) = 1.5 mg.

vasodilatation, there was no significant alteration in the majority. In the anesthetized animal, however, the intravenous administration of similar doses of reserpine produced an immediate effect on the blood pressure which was often transient but which sometimes persisted in some degree for a considerable period. This immediate effect was independent of the anesthetic used, although there was a larger fall from the high pressure usual with chloralose than occurred from the lower pressures recorded with barbiturate anesthesia. The upper record in figure 3 shows the fall in systemic blood pressure in a gray rabbit weighing 1.5 Kg., anesthetized with chloralose (100 mg. per kilogram) after intravenous injection of 1.5 mg. of reserpine in 0.6 ml. of solvent. The effect of a control injection of the solvent* is also shown. Figure 4 shows the effect of 2.5 mg. of reserpine in 2.5 ml. of a solvent consisting of a 1:1:2 mixture of ethyl alcohol, propylene glycol and water[7] on intravenous injection into a 2 Kg. gray rabbit anesthetized with Nembutal-urethane (90 mg. Nembutal and 750 mg. urethane intraperitoneally). The effect of control injection of this solvent is also shown.

* Vehicle for Serpasil, supplied by Ciba Ltd., Basle; formula not disclosed.

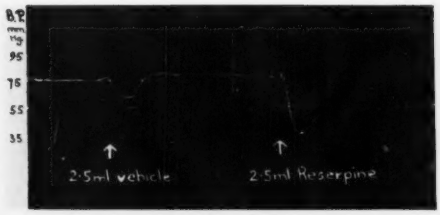


FIG. 4. Gray rabbit, 2 Kg. Blood pressure changes (scale on left in mm. Hg) after 2.5 ml. of a solvent consisting of a 1:1:2 mixture of ethyl alcohol, propylene glycol and water, and after 2.5 ml. of the same solvent containing 2.5 mg. reserpine.

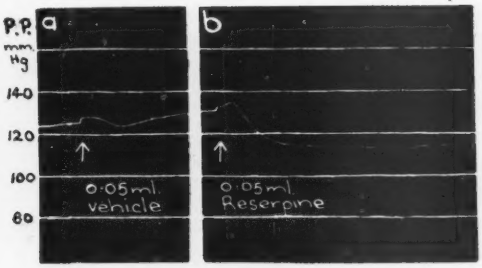


FIG. 5. Gray rabbit. Perfusion pressure in isolated innervated hind limb. Vehicle (in this case that supplied by Ciba) injected at point shown by the first arrow, 0.125 mg. reserpine in 0.05 ml. of the same vehicle injected at the point shown by the second arrow.

In order to investigate the mechanism of action of this direct effect a series of limb perfusion experiments was carried out according to the method of Gallagher.[12] With this technic the nerve supply to the hind limb is preserved but all vascular communications with the rest of the body are interrupted. A red cell–dextran medium is perfused through the limb via the femoral artery by a pump which delivers the medium at constant rate regardless of pressure. Variations of vasomotor tone are indicated by variations in perfusion pressure. In figure 3 the lower record is the perfusion pressure. Intravenous injection of 1.5 mg. reserpine, as seen previously, caused a marked fall in systemic blood pressure, and this was accompanied by a marked and prolonged rise in perfusion pressure, indicating an increase in nervous tone in the perfused limb.

The effect of injection of 0.125 mg. of reserpine into the perfusion cannula is shown in figure 5. There is an immediate fall in pressure of prolonged duration.

In Cats. The immediate fall in blood pressure which occurred with large doses in anesthetized rabbits occurred also on occasion in cats. However, in cats there was a prolonged hypotensive effect of delayed onset similar to the hypotensive action of reserpine in man. The delayed effect did not occur invariably and appeared to bear a relationship to the level of the initial blood pressure, being marked in animals with a high initial pressure and smaller in animals with lower initial pressures.

Evidence for the central nervous action of Rauwolfia alkaloids has been adduced by Dasgupta and co-workers[3] in the greatly augmented response to a solution of total alkaloids when given intracisternally rather than intravenously. Reserpine is insoluble except in highly acid or irritating solvents and the intracisternal injection of small amounts of either of the above-mentioned solvents produced such manifestations as convulsions, sudden death or extreme rises or falls in blood pressure. Because of the effects of the solvents, those of reserpine could not be studied.

In six experiments using either cats or rabbits, reserpine was injected into the subclavian artery on one side so that all the injected material passed up the vertebral artery. A cannula was inserted into the subclavian artery distal to the origin of the vertebral artery so that injections could be made in a cephalic direction. During injections the subclavian artery was clamped proximal to the origin of the vertebral artery, the clamp being released after the injection had been given. When 0.25 mg. of reserpine was injected in this manner no significant hypotensive effect was produced in any of the six experiments. By contrast, injections of 0.1 mg. of ester alkaloid fraction of veratrum viride* given in the same way produced in some preparations immediate large falls of blood pressure.

(c) *Modification of Reflex Cardiovascular Responses by Reserpine*

As has been stated in the preceding paragraphs, the prolonged hypotensive effect of

* Anatensol, Squibb.

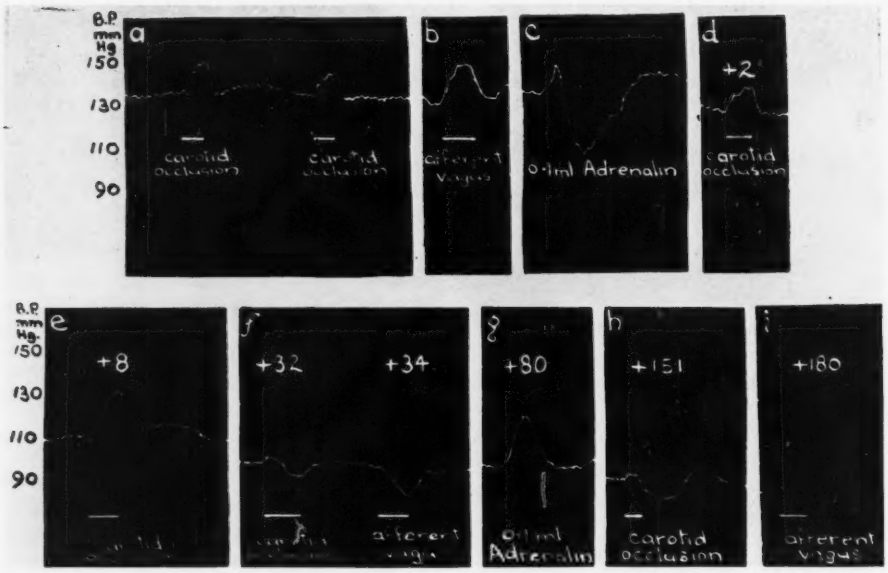


FIG. 6. Cat, 3.5 Kg. Chloralose. Blood pressure record, left femoral artery. *a*, *b* and *c* show responses to stimuli before administration of reserpine, *d* to *i* the responses to the same stimuli after reserpine. Between *c* and *d*, 2.5 mg. reserpine injected intravenously. Carotid occlusion was repeated two minutes after injection of reserpine, and subsequent stimuli were applied at 8, 32, 34, etc., minutes after the injection of reserpine, as shown in the upper part of each figure.

delayed onset, such as that which occurs with reserpine in hypertensive patients, is frequently not seen to any clearly marked degree in rabbits or cats. A series of further experiments was performed to assess the extent to which reserpine may modify various reflex cardiovascular responses. The effects of occlusion of the carotid arteries, stimulation of the afferent vagus, and the administration of adrenaline were studied in cats. The results are exemplified in figure 6. In this figure is shown the responses in a 3.5 Kg. cat anesthetized with chloralose. Blood pressure was recorded by a cannula in the left femoral artery. Both carotid arteries were isolated and a piece of braided silk looped behind each. Gentle traction on these pieces of silk permitted occlusion of the arteries. The vagus nerve on the right side was isolated and cut and the cephalic end placed over a pair of silver electrodes moistened with saline. Electrical stimuli were applied at a constant rate of eight shocks per second. Adrenaline was administered intravenously in doses of 1.0 μg. It will be seen that the initial marked pressor responses to bilateral carotid occlusion were still present two and eight minutes after 2.5 mg. reserpine intravenously, but were thereafter modified so that the rise in pressure was very much diminished in amplitude and was maintained for only a brief period, being succeeded by a fall. The fall in blood pressure followed a marked slowing of the pulse. Afferent vagal stimulation initially produced a markedly pressor response. At 34 minutes after reserpine the response to the same stimulus was depressor and remained so at 180 minutes. The initial response to adrenaline was biphasic, the initial pressor effect being followed by a marked fall in blood pressure presumably of reflex origin. After reserpine, the reflex depressor element disappeared so that adrenaline produced a purely pressor response.

In rabbits the effects of electrical stimulation of the cephalic end of the cut vagus and of injection of adrenaline before and after reserpine were studied in similar fashion. There is marked difference in species response between rabbits and cats. However, the capacity of reserpine

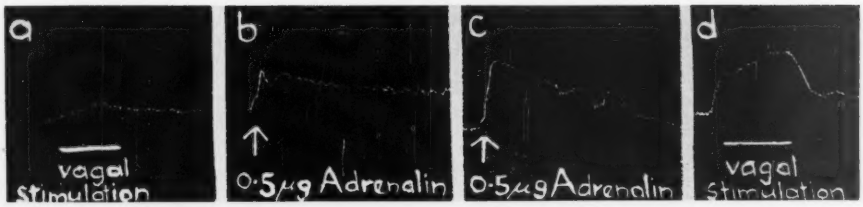


FIG. 7. Gray rabbit, 1.5 Kg. Chloralose. Blood pressure record, right carotid artery. In *a* cephalic end of cut vagus stimulated. In *b* 0.5 μg. adrenaline injected intravenously. Immediately after *b* 1.5 mg. reserpine injected intravenously; 60 minutes allowed to elapse before (*c*) intravenous injection 0.5 μg. adrenaline, and (*d*) stimulation of cephalic end of vagus repeated.

to modify the responses was again demonstrated. Blood pressure was recorded from one carotid artery, and the vagus nerve of the same side isolated and cut low in the neck. Electrical stimulation before reserpine produced a minimal effect with slight rise in blood pressure. After reserpine there was a marked rise. Extreme tachycardia accompanied the rise in blood pressure. These results are illustrated in figure 7 which shows the effect of stimulation of the cephalic end of the cut vagus before and after reserpine (1.5 mg. intravenously), in a 1.5 Kg. gray rabbit anesthetized with chloralose. The rabbits invariably responded to adrenaline by a rise of pressure, but following reserpine the rise was of considerably greater magnitude (fig. 7).

DISCUSSION

One of the difficulties of assessing the site of action of reserpine in normotensive animals is that in these, as in normotensive man, the falls of blood pressure are often inconspicuous or absent. In both normotensive and hypertensive man, however, the facial flushing which precedes the fall of blood pressure occurs to a similar degree, and in rabbits a similar flushing of the ears occurs. Our results seem to indicate that the vasodilatation observed in the rabbit's ear is mediated through the sympathetic nervous system since in the denervated ear the vasodilatation seen in the innervated ear did not occur. There is, therefore, strong evidence that part at least of the peripheral vasodilating action of reserpine is mediated through the sympathetic nervous system.

Prolonged hypotensive effects from reserpine, such as are seen in hypertensive man are, in experimental animals as in normotensive man, of small order and inconsistent. It is thus difficult to demonstrate that the hypotensive effect of reserpine is similarly mediated via the sympathetic nervous system. Reserpine was found, however, to produce a profound modification of certain reflex vasomotor responses. In cats the effect of occlusion of the carotid arteries was abolished or even reversed; the pressor response to electrical stimulation of the cephalic end of the cut vagus was converted to a depressor response and the reflex (depressor) sequel of adrenaline injection abolished so that the action of adrenaline became purely pressor.

In rabbits also the effect of electrical stimulation of the proximal end of the cut vagus was greatly modified as was also the effect of an injection of adrenaline, the latter it seems reasonable to suggest, by suppression of the reflex nervous mechanism tending to minimize the pressor effect.

Modification of reflex vasomotor responses of various kinds by Rauwolfia derivatives has been demonstrated by most workers,[1, 2, 3, 6, 7] and it is considered by Trapold and associates[7] that the hypotensive effect of reserpine is due to central inhibition of reflex pressor sympathetic activity. The present series of experiments gives further evidence of an inhibitory effect on reflex vasomotor activity.

It has thus been shown that reserpine acts through the sympathetic nervous system to produce cutaneous vasodilatation and also modification of vasomotor reflex responses. It seems reasonable to assume, therefore, that reserpine produces its hypotensive action in part through the mediation of the sympathetic

nervous system. There is, however, evidence that the hypotensive effect cannot be solely ascribed to this action. In the limb-perfusion experiments performed by us the fall of systemic pressure which occurred immediately after the intravenous injection of reserpine was accompanied by a marked rise of pressure in the perfused hind limb, indicating an increase in vasomotor tone. Were the fall of systemic blood pressure solely the result of inhibition of the sympathetic nervous system, it would have been expected that the perfusion pressure in the limb would also have fallen. The fact that the perfusion pressure rose suggests that compensatory nervous mechanisms had become active in response to a fall of blood pressure resulting from a nonnervous cause.[12] The production of vasodilatation by injection of reserpine directly into the perfused innervated hind limb demonstrates that reserpine has a direct action on the vessels in the rabbit.

In man, ganglionic blockade with hexamethonium produced a lower blood pressure after reserpine had been given than before. Unless there are autonomic nervous pathways unaffected by hexamethonium in man, this seems to suggest that the hypotensive effect of reserpine does not occur exclusively through the sympathetic nervous system. It seems that in man, as in rabbits and possibly cats, reserpine may have a peripheral vasodilating effect in addition to an effect mediated through the sympathetic nervous system.

Summary

The hypotensive effects of large doses of reserpine have been studied in 33 hypertensive patients and in 12 subjects with normal blood pressure. In the hypertensives, the fall of blood pressure varied from that to be expected with placebos to large falls, occasionally to normal levels. In normotensives blood pressure falls were much smaller. The fall of blood pressure is accompanied by cutaneous vasodilatation. Cutaneous vasodilatation is also seen in animals; its abolition by severance of the cervical sympathetic chain shows that this effect is mediated via the sympathetic nervous system. Modification of reflex vasomotor responses occurs in both rabbits and cats. However in anesthetized rabbits a direct vasodilator effect on blood vessels is shown and evidence is put forward that reserpine may have a direct peripheral vasodilating effect in man.

Acknowledgment

We are grateful to Ciba Ltd., Basle, for supplies of reserpine (Serpasil) and the vehicle in which Serpasil is supplied.

Summario in Interlingua

Le effectos hypotensive de grande doses de reserpina esseva studiate in 33 patientes hypertensive e in 12 sujectos con pression sanguinee normal. In le hypertensivos le reduction del pression sanguinee producite per le administration de reserpina variava inter le non-significative grados que poterea esser expectate ab le administration de remedios fictive e abassamentos marcate que attingeva in alicun casos nivellos normal. In normotensivos le reduction del pression sanguinee esseva multo plus parve. Le reduction del pression sanguinee es accompaniate de vasodilatation cutanee. Un tal es etiam observate in animales. Le facto que illo pote esser supprimite per le section del sympathic catena cervical demonstra que iste effecto es mediate via le sympathic systema nervose. Modificationes del responsas vasomotor reflexe occurre tanto in conilios como etiam in cattos. Nonobstante, in conilios anesthesiate un directe effecto vasodilatatori super le vasos sanguinee es demonstrabile. Nos presenta datos que pare indicar que reserpina ha un directe effecto vasodilatatori peripheric in homines.

REFERENCES

[1] Chopra, R. N., Gupta, J. C., and Mukherjee, B.: The pharmacological action of an alkaloid obtained from *Rauwolfia serpentina*, Benth. Indian J. M. Res. **21:** 261, 1933.

[2] Ray, G. K., Roy, P. K., Dasgupta, S. R., and Werner, G.: The action of *Rauwolfia serpentina* on vasomotor reflexes. Arch. exper. Path. u. Pharmakol. **219:** 310, 1953.

[3] Dasgupta, S. R., Ray, G. K., and Werner, G.: Central actions of *Rauwolfia serpentina*. Indian J. M. Sc. **7:** 597, 1953.

[4] Müller, J. M., Schlittler, E., and Bein, H.

J.: Reserpin, the sedative principle from *Rauwolfia serpentina* Benth. Experientia **8:** 338, 1952.

[5] BEIN, H. J., GROSS, F., TRIPOD, J., AND MEIER, R.: Experimentelle Untersuchungen über "Serpasil" (Reserpin), ein neues, sehr wirksames Rauwolfiaalkaloid mit neurartiger zentraler Wirkung. Schweiz. med. Wchnschr. **83:** 1007, 1953.

[6] —: Zur Pharmakologie des Reserpin, eines neuen Alkaloids aus *Rauwolfia serpentina* Benth. Experientia **9:** 107, 1953.

[7] TRAPOLD, J. H., PLUMMER, A. J., AND YONKMAN, F. F.: Cardiovascular and respiratory effects of Serpasil, a new crystalline alkaloid from *Rauwolfia serpentina* Benth, in the dog. J. Pharmacol. **110:** 205, 1954.

[8] WAGENER, H. P., AND KEITH, N. M.: Diffuse arteriolar disease with hypertension and the associated retinal lesions. Medicine **18:** 317, 1939.

[9] DOYLE, A. E., AND SMIRK, F. H.: The use of the pure veratrum alkaloids neogermitrine and protoveratrine in hypertension. Brit. Heart J. **15:** 439, 1953.

[10] —, McQUEEN, E. G., AND SMIRK, F. H.: Treatment of hypertension with reserpine, with reserpine in combination with pentapyrrolidinium, and with reserpine in combination with veratrum alkaloids. Circulation **11:** 170, 1955.

[11] GRANT, R. T., AND ROTHSCHILD, P.: A device for estimating blood-pressure in the rabbit. J. Physiol. **81:** 265, 1934.

[12] GALLAGHER, D. J. A.: A medium for perfusion of innervated blood vessels. Brit. J. Pharmacol. **9:** 129, 1954.

Treatment of Hypertension with Reserpine, with Reserpine in Combination with Pentapyrrolidinium, and with Reserpine in Combination with Veratrum Alkaloids

By A. E. Doyle, M.D., M.R.C.P., E. G. McQueen, M.B., M.R.C.P., and F. H. Smirk, M.D., F.R.C.P.

The treatment of hypertension with reserpine is described. When used alone it produced adequate falls of blood pressure in ten out of forty patients. The combination of reserpine with veratrum did not increase the hypotensive effects of reserpine alone. The combination of reserpine with pentapyrrolidinium increases the effectiveness of the pentapyrrolidinium and lessens its parasympathetic side effects. The combination of reserpine and pentapyrrolidinium is regarded as the best therapeutic regime for severe hypertension. Some mild cases of hypertension may be managed with reserpine alone.

EXTRACTS of *Rauwolfia serpentina* have been extensively used in India for several decades in the treatment of a variety of conditions including hypertension.[1] Their value in treatment of the latter condition has recently attracted world-wide interest. The particular activity as a hypotensive agent of reserpine, an alkaloid of Rauwolfia isolated by Swiss workers[2] has been investigated in animals by Bein and associates,[3, 4] Trapold and co-workers,[5] Plummer and colleagues,[6] and McQueen and associates.[7] These studies have indicated that in part at least, the hypotensive action of reserpine is mediated through the sympathetic nervous system. Our own studies[7] have also shown that in rabbits reserpine has a direct vasodilating action on the blood vessels and suggest that there may be some direct effect in man. In a previous report from this department[8] the effects of large doses of reserpine in man were described, and further clinical studies have been published by Löffler and co-workers[9], Wilkins,[10, 11] Freis and Ari,[12] Hafkenschiel and Sellers,[13] Winsor,[14] and Moyer.[15]

From the Department of Medicine, Otago University Medical School, Dunedin, New Zealand.

This work was supported in part by the Life Insurance Medical Research Fund of Australia and New Zealand and in part by the Medical Research Council of New Zealand.

The use of Rauwolfia alkaloids in combination with other hypotensive agents has been reported on by Wilkins[10] (Serpina and Apresoline), Wilkins and Judson[16] (Serpina and veratrum alkaloids) and Ford and Moyer[17] (Rauwiloid and hexamethonium). A preliminary account[18] has outlined in general terms our own experiences with a combination of reserpine and pentapyrrolidinium. At that time it could be stated that of 40 cases, distinctive benefits had resulted from the use of the combination in 27 (8 classified as very good and 19 as good). Benefit was apparent either in an important decrease of side effects or in improvement in the degree of blood pressure control without increase of side effects, or in a combination of these. Eight were classed as fair, meaning that some specific advantage had been obtained by the combination although this might be of slight degree. In only 5 out of 40 were the results considered poor. It was pointed out that an important advantage of the combination of reserpine and pentapyrrolidinium is that the dose of the latter is smaller than would be needed if it were used alone to produce an equal hypotensive action.

In the present report the results are presented of using reserpine alone in tolerable doses in 40 cases, reserpine in combination with pentapyrrolidinium in 66 cases, with hexamethonium in 9 cases, and in combination with alkaloids of veratrum in 10 cases.

Results

Reserpine Alone

Reserpine in doses of 9 mg. daily will reduce the blood pressure in most hypertensive subjects.[8] Such large doses are accompanied by side effects of a degree of severity such as to make their use as a form of continuous therapy impractical. In a certain number of cases, however, the blood pressure is substantially reduced at a dosage level low enough to avoid serious side effects (0.5 to 1.5 mg. per day). We have given 40 patients a trial of therapy with reserpine alone in this dosage. In 10 of these blood pressure control was sufficiently good for it to be used as the treatment of choice. In several further patients good falls were obtained with low doses but blood pressure control was not as satisfactory as could be obtained by the addition of small amounts of another hypotensive agent, usually pentapyrrolidinium. Table 1 shows the 10 cases who have been treated with reserpine alone as the therapy of choice. Although in general the cases were relatively mild, several were of considerable severity. The fact that the blood pressure range whilst on reserpine extends well below the basal blood pressure[19] in all cases in which the latter was recorded, suggests that reserpine is exerting an active hypotensive effect and that the blood pressure falls are not merely psychologic or sedative in origin.

Side Effects. The side effects of large doses of reserpine have been detailed by Doyle and Smirk[8]; they consist of conspicuous conjunctival injection, nasal blockage, sensations of fatigue and sleepiness, depression, shivering, and occasional restlessness. With doses of the order of 0.5 to 1.5 mg. a day, such as we have used for continued therapy with reserpine alone and in combination with pentapyrrolidinium and veratrum preparations, similar side effects are still frequently encountered, and although of lesser severity, may at times prohibit its use. Other side effects we have encountered with these doses are diarrhea, which is the most troublesome one, undue susceptibility to cold, excessive gains in weight, and nightmares. These side effects, although at times troublesome, are not as a rule sufficiently severe to prevent the use of the drug. We have, however, noticed that in some patients associated conditions not closely connected with the hypertension have been aggravated. This applies particularly to patients with pre-existing depressive states. We have also noticed

Table 1.—*Effects on the Blood Pressure of Reserpine*

No.	Grade	Age	Basal B.P.	Dose reserpine (mg.)	B.P. range* before reserpine	B.P. range* after reserpine	Side effects
16	II	53	154/102	0.5 t.i.d.	220/160–190/120	170/100–120/70	Coexisting ulcerative colitis somewhat aggravated, dyspnea
363	II	37	163/94	1.5 a.m. 0.5 noon 1.5 p.m.	180/140–170/100	110/70 –100/60	Minimal
733	II	46	144/86	4.0 per day	190/120–170/110	160/90 –130/70	Somnolence
756	I (+ angina pectoris)	46	Not recorded	0.5 t.i.d.	Approx. 150/110	120/90 –88/70	None
766	I	50	166/116	1.5 t.i.d.	Clinic casual 214/138	160/80 –110/80	Somnolence, nausea
768	II	46	152/96	0.25 b.d.	175/100–155/90	130/80 –120/80	Depression
776	II	63	196/124	0.5 t.i.d.	210/130–190/140	170/100–130/80	Bronchospasm
787	III	37	130/90	0.5 t.i.d.	160/110–130/90	150/100–105/75	None
908	II	46	160/100	0.25 t.i.d.	190/110–160/100	140/100–120/80	None
915	II	64	Not recorded	1.0 b.d.	230/130–160/120	190/100–140/70	Diarrhea, shivering. Cardiac failure progressed while on treatment

* Range of blood pressure refers to the highest and lowest blood pressure readings recorded during a day spent in the clinic.

TABLE 2.—*Effects on the Blood Pressure and the Incidence of Side Effects of Reserpine and Pentapyrrolidinium*

No.	Previous dose pentapyrrolidinium (mg.)	Present dose pentapyrrolidinium (mg.)	Dose reserpine (mg.)	B. P. control after reserpine	Previous side effects pentapyrrolidinium	Present side effects pentapyrrolidinium	Side effects reserpine	Classification‡ of results	Sitting B. P.		Standing B. P.	
									Range* before reserpine	Range after reserpine	Range before reserpine	Range after reserpine
16	400 daily orally	180 daily orally (Later maintained on reserpine alone)	0.5 t.i.d.	Improved	Nausea	Diminished	None	*Good*	220/160–190/150	152/102–116/80	220/170–140/100	124/80–76/?
17	Hexamethonium† 2½ tabs. t.i.d.	Hexamethonium 2½ tabs. t.i.d.	0.5 t.i.d.	Improved	Dry mouth, blurred vision	No change	Somnolence	*Fair*	208/120–162/90	188/72–136/80	204/120–160/110	188/72–122/68
25	4.8 b.d. subcutaneously	No change Now 80 orally	0.5 t.i.d.	Much improved	Vomiting, severe dryness of mouth, severe constipation	No vomiting, less dry mouth, constipation relieved	None	*Very Good*				
32	920 daily orally	920 daily orally	0.5 b.d.	Improved	Dryness of mouth	Unchanged	Flushing of face, lassitude	*Fair*	206/130–134/98	152/82–100/72	180/110–110/80	120/68–82/60
41	34 b.d. subcutaneously	26.5 b.d.	1.0 b.d.	Improved	Diarrhea, constipation	None	None	*Good*				
51	28 b.d. subcutaneously	26 b.d.	3.0 t.i.d.	Unchanged	Dry mouth	Unchanged	Somnolence	*Poor*	206/140–120/75	230/154–110/60	192/130–130/100	230/140–116/70
86	16.5 b.d. subcutaneously	11 b.d. subcutaneously	0.5 b.d.	Improved	Dryness of mouth, blurred vision, constipation. Occasional slight shivering 2 hours after injection	Constipation improved, otherwise no change. Duration side effects less	Shivering unassociated with sensation of coldness	*Fair*				
98	230 daily orally	80 daily orally	0.5 t.i.d.	Improved	Dryness of mouth	None	Biliary colic necessitating withdrawal	*Poor*	198/136–156/98	186/80–146/104	194/132–148/100	162/116–140/116
105	Hexamethonium† 160 t.i.d. subcutaneously	Hexamethonium 160 t.i.d. subcutaneously	1.5 t.i.d.	Worse. Subsequently better controlled pentapyrrolidinium orally	Dry mouth, blurred vision	No change	None	*Poor*	238/168–158/110	238/142–200/130	238/160–170/122	250/154–200/122
110	50 b.d. subcutaneously + 720 daily orally	780 daily orally	3.5 at night	Improved	Extreme dryness of mouth, blurred vision	Diminished	None	*Very Good*	248/142–108/74	192/118–92/60		194/129–92/60
124	Hexamethonium† 20 b.d. subcutaneously	Hexamethonium 20 b.d. (Subsequently well managed on reserpine-pentapyrrolidinium)	1.5 b.d.	Unchanged	Dryness of mouth, blurred vision, constipation	Unchanged	None	*Poor*	240/138–162/120	220/142–160/98	220/140–162/116	204/116–148/98

* Range of blood pressure refers to the highest and lowest blood pressure readings recorded during a day spent in the clinic.

† Except where indicated figures in these columns refer to pentapyrrolidinium.

‡ Classification is based on the extent to which addition of reserpine has improved management with pentapyrrolidinium. "Very good" and "good" signify a distinctive benefit from the combination, apparent either in an important decrease in side effects or in improvement in the degree of blood pressure control without increase in side effects, or in a combination of these. "Fair" means that some specific advantage was obtained by adding reserpine. "Poor" means that management was no better or was worse after adding reserpine.

129	290 a.m., 40 noon, 140 p.m., orally	160 a.m., 40 noon, 200 p.m., orally	0.5 t.i.d.	Unchanged	Blurred vision, dryness of mouth	Aggravated whilst on reserpine	Severe flushing (starting menopause)	*Poor*				
153	160 b.d. orally	100 b.d. orally	0.5 b.d.	Improved	Blurred vision, dryness of mouth, constipation	Vision unchanged, mouth better	Shivering, diarrhea (mild only)	*Fair*				
164	18 b.d. subcutaneously	18 b.d.	2.0 b.d.	Improved	Dryness of mouth, blurred vision	Diminished	None	*Good*	260/180–210/140	198/120–160/106	270/190–194/130	192/124–140/100
171	30 b.d. subcutaneously 360 orally	23 b.d. subcutaneously 240 orally	0.5 t.i.d.	Improved	Dryness of mouth, constipation	Mouth unchanged, constipation better	None	*Good*				
194	180 daily orally	105 daily orally	0.25 t.i.d.	Improved	Dryness of mouth, severe constipation	Mouth improved	Diarrhea	*Good*	234/134–148/102	188/104–126/76	240/148–132/96	142/80–120/70
195	7 b.d. subcutaneously	3.5 b.d.	0.5 t.i.d.	Unchanged	Blurred vision, dryness of mouth, constipation	Diminished	None	*Good*	206/110–160/90	202/110–160/86	204/104–152/62	218/122–162/80
204	24.5 b.d. subcutaneously	10.0 b.d.	0.5 b.d.	Unchanged	Dryness of mouth, blurred vision	All improved	None	*Fair*				
207	920 a.m., 280 noon, 320 p.m., orally	880 a.m., 400 p.m., orally	0.5 b.d.	Improved	Blurred vision, dryness of mouth	Much improved	Shivering and sensation of coldness. Sleeping very deeply and dreaming frequently, slight diarrhea	*Good*				
232	25 a.m. 27.5 p.m. subcutaneously	10 a.m. 27.5 p.m. Changed to oral pentapyrrolidinium	0.5 b.d.	Unchanged	Dryness of mouth, blurred vision. *No* constipation. Slight shakiness after injection	No dryness of mouth or blurred vision	None					
		Final régime: 100 a.m., 80 noon, 100 p.m.	Final régime: 0.5 a.m., 0.5 noon, 1.0 p.m.	Final régime: very satisfactory. No numerical assessment possible	Constipation	Constipation relieved by increase in reserpine	Shivering	*Good*				
236	Hexamethonium† 200 t.i.d. subcutaneously	Pentapyrrolidinium 40 a.m., 20 noon, 40 p.m., orally	0.5 b.d.	Improved	Dryness of mouth, blurred vision, constipation	None	None	*Very Good*	184/120–138/92	138/90–124/80	170/140–126/90	148/90–126/76
242	Hexamethonium† tabs. 5 t.i.d.	Hexamethonium tabs. 5 t.i.d.	2 b.d.	Improved	Dryness of mouth, blurred vision, constipation	No change	Bronchial asthma	*Poor*	192/132–144/96	168/76–110/54	204/138–144/92	162/52–105/56
243	Hexamethonium† 210 b.d. subcutaneously and 4 tabs. orally	Hexamethonium 165 b.d. subcutaneously and 4 tabs. orally	1.0 b.d.	Improved	Dryness of mouth	Diminished	Depression	*Good*				
246	360 daily orally	120 daily orally	0.5 b.d.	Improved	Dryness of mouth, dimness of vision, constipation	All improved	None	*Very Good*	222/122–180/100	176/108–150/80	218/120–174/100	170/120–138/100

TABLE 2.—(*Continued*)

No.	Previous dose pentapyrrolidinium (mg.)	Present dose pentapyrrolidinium (mg.)	Dose reserpine (mg.)	B. P. control after reserpine	Previous side effects pentapyrrolidinium	Present side effects pentapyrrolidinium	Side effects reserpine	Classification‡ of results	Sitting B. P.		Standing B. P.	
									Range* before reserpine	Range after reserpine	Range before reserpine	Range after reserpine
261	Hexamethonium† 100 b.d. subcutaneously	Hexamethonium 100 b.d. subcutaneously	0.25 b.d.	Improved	Diarrhea	None	None	*Good*				
264	220 a.m., 260 p.m. orally	220 b.d. orally	0.5 b.d.	Improved	Blurred vision	Eyes improved, increased dryness of mouth	Flushed face, eyes slightly injected, shivering	*Fair*				
273	9 a.m., 10 p.m. subcutaneously	9 a.m., 10 p.m. subcutaneously	0.5 b.d.	Much improved	Blurred vision	Eyes improved, dryness of mouth	Shivering	*Fair*				
294	240 a.m., 140 noon, 280 p.m. orally	180 a.m., 120 noon, 220 p.m. orally	0.5 b.d.	Improved	Blurred vision, dryness of mouth, constipation	All much improved	Lassitude, shivering	*Very Good*				
304	7 a.m., 9 p.m., subcutaneously	2.5 a.m., 5.0 p.m.	0.25 t.i.d.	Much improved	Blurred vision, dryness of mouth, constipation, severe impairment potency	Blurred vision, dryness improved. Constipation, impotence unaltered	Slight shivering after injection	*Very Good*	204/140–122/80	205/120–100/70	210/130–118/80	170/120–90/50
307	280 a.m., 320 p.m. orally	120 a.m., 160 p.m. orally	0.5 b.d.	Improved	Blurred vision, dryness of mouth	Slight blurring only, no dryness	Nasal obstruction, marked gain in weight	*Good*				
308	340 a.m., 120 noon, 360 p.m. orally	140 a.m., 80 noon, 140 p.m. orally	0.5 t.i.d.	Improved	Dryness of mouth, blurred vision, constipation	Lessened	Shivering marked	*Fair*	200/102–148/88	196/102–112/64	186/102–156/92	180/102–108/68
313	15.5 a.m., 16.0 p.m. subcutaneously	13.0 b.d.	0.5 b.d.	Improved	Dryness of mouth, constipation	Improved	Nasal obstruction	*Fair*				
320	6.4 a.m., 10.0 p.m. subcutaneously	4 b.d.	0.75 b.d.	Improved	Dryness of mouth, blurred vision	Unchanged	None	*Good*				
336	8 a.m., 17 p.m. subcutaneously	8 a.m., 17 p.m. subcutaneously	0.5 t.i.d.	Improved	None	None	Shivering	*Good*	212/128–186/118	194/116–140/102	228/132–200/124	198/124–152/108
339	480 a.m., 500 p.m. orally	440 a.m., 460 p.m. orally	0.5 b.d.	Improved	Dryness of mouth, constipation	Dryness of mouth	Diarrhea	*Fair*				
344	55 b.d. subcutaneously	33 b.d.	0.5 t.i.d.	Much improved	Dryness of mouth, nausea, impotence	Mouth improved, no nausea, impotence unchanged	None	*Very Good*				
350	12.8 b.d. subcutaneously	12.8 b.d.	1.5 b.d.	Improved	Dryness and soreness of mouth, anorexia	Much improved	None	*Very Good*	220/160–142/82	186/122–142/100	230/166–148/100	186/142–126/80
354	40 t.i.d. orally	30 b.d. orally	0.5 t.i.d.	Improved	Dryness of mouth, anorexia, constipation	All much improved	Lassitude, gain 7 lbs.	*Very Good*				
361	320 a.m., 680 noon, 900 p.m. orally	180 a.m., 180 noon, 40 p.m. orally	0.5 b.d.	Improved	Dryness of mouth, blurred vision, constipation	Less dryness and blurring, constipation persists	Lassitude, gain 6 lbs.	*Very Good*				

365	30 b.d. subcutaneously	16 b.d.	0.5 t.i.d.	Unchanged	Very severe dryness of mouth	Much improved	Somnolence	*Good*				
376	12.5 a.m., 13.5 p.m. subcutaneously	12.5 a.m., 13.5 p.m. subcutaneously	0.5 t.i.d.	Improved	Blurred vision, dryness of mouth	Unchanged	Shivering	*Poor*				
391	120 a.m., 80 noon, 140 p.m. orally	120 a.m., 80 noon, 140 p.m. orally	0.5 b.d.	Improved	None	None	None	*Fair*				
400	480 a.m., 600 noon, 480 p.m. orally	200 a.m., 480 noon, 200 p.m. orally	0.5 b.d.	Improved	Dryness of mouth, blurred vision	Much improved, gaining weight for first time on treatment	None	*Very Good*				
717	12 b.d. subcutaneously	5 b.d.	0.5 b.d.	Improved	Blurred vision, dryness of mouth, impotence	Relieved except impotence	Lassitude, restlessness, nasal obstruction	*Good*				
721	84 b.d. subcutaneously	88 b.d.	2.0 b.d.	Unchanged	Dryness of mouth, blurred vision, constipation	Unchanged	None	*Initially Good, Now Poor*	188/122–128/82	230/160–144/122		
730	200 a.m., 240 p.m. orally	170 a.m., 200 p.m. orally	0.5 b.d.	Improved	Blurred vision, dryness of mouth	Unchanged	Shivering, somnolence	*Poor*				
732	28 b.d. subcutaneously	200 a.m., 80 noon, 240 p.m. orally	0.5 t.i.d.	Unchanged	Dryness of mouth, blurred vision	Improved	None	*Fair*	220/120–120/60	192/100–140/78	238/130–100/58	188/108–154/90
737	210 b.d. orally	100 a.m., 120 p.m., orally	0.5 b.d.	Much improved	Blurred vision, dryness of mouth, constipation	All virtually abolished	None	*Very Good*	198/138–144/100	186/122–120/80	192/132–134/96	192/126–126/72
743	340 a.m., 80 noon, 340 p.m. orally	340 a.m., 80 noon, 340 p.m. orally	0.5 b.d.	Unchanged	Blurred vision, dryness of mouth	Unchanged	Diarrhea	*Poor*				
745	220 b.d. orally	220 b.d. orally	0.25 b.d.	Improved	Constipation	None	Gain in weight, recurrence exertional dyspnea	*Poor*				
749	65 b.d. subcutaneously	60 b.d. subsequently became resistant	3.0 t.i.d.	Temporarily improved	Blurred vision, dryness of mouth, constipation	Unchanged	Depression	*Poor*				
753	35.5 b.d. subcutaneously	33 b.d.	0.5 b.d.	Improved	Dyrness of mouth	Diminished	None	*Very Good*				
755	15 b.d. subcutaneously	10 b.d.	0.5 b.d.	Unchanged	None	None	Severe exacerbation pre-existing depression	*Poor*				
757		190 a.m., 40 ncon, 190 p.m. orally	0.5 t.i.d.	Satisfactory				*Satisfactory Régime*		210/110–136/76		196/110–146/80
761	Hexamethonium† 34 b.d. subcutaneously	Pentapyrrolidium 80 a.m., 120 p.m., orally	0.5 t.i.d.	Improved	Mild diarrhea	Increased severity, diarrhea	Nightmares, shivering	*Fair*				
763	Hexamethonium† 40 t.i.d. subcutaneously	Hexamethonium 40 t.i.d.	2.0 b.d.	Unchanged	None	None	Shaking, shivering	*Poor*	160/120–128/100	180/140–152/110	172/134–120/94	198/156–162/120
770	180 b.d. orally	180 b.d. orally	0.5 daily	Improved	None	None	Generally miserable, legs aching, nasal obstruction, ? bronchospasm. Side effects precluded use	*Poor*	184/102–134/76	176/122–124/82	184/128–132/104	170/118–132/100

TABLE 2.—(*Continued*)

No.	Previous dose pentapyrrolidinium (mg.)	Present dose pentapyrrolidinium (mg.)	Dose reserpine (mg.)	B. P. control after reserpine	Previous side effects pentapyrrolidinium	Present side effects pentapyrrolidinium	Side effects reserpine	Classification‡ of results	Sitting B. P.		Standing B. P.	
									Range* before reserpine	Range after reserpine	Range before reserpine	Range after reserpine
775	26 b.d. subcutaneously	18 b.d.	0.5 b.d.	Improved	Dryness of mouth	None	Nightmares, shivering	*Good*	238/140–110/62	220/118–112/72	250/128–92/50	210/100–98/68
780	12.5 b.d. subcutaneously	13.5 b.d.	1.0 b.d.	Improved	Blurred vision, dryness of mouth, constipation	Unchanged	None	*Fair*	280/140–170/110	208/120–150/84	240/130–120/90	190/130–120/90
781	32 b.d. subcutaneously	19 b.d.	0.5 t.i.d.	Improved	Dryness of mouth, blurred vision	Diminished	None	*Good*	226/150–130/100	160/110–114/76	190/152–118/74	142/98–96/60
785	15 b.d. subcutaneously	8 b.d.	0.5 t.i.d.	Improved	None	None	None	*Fair*	204/130–140/102	152/114–82/54	204/128–140/102	142/102–68/50
790	280 a.m., 40 noon, 280 p.m. orally	200 a.m., 60 noon, 200 p.m. orally	0.5 t.i.d.	Unchanged	Constipation, dryness of mouth, blurred vision	Unchanged	Depression	*Fair*	224/120–180/90	168/94–140/78	220/116–162/80	160/90–128/60
792	23 b.d. subcutaneously	14 b.d. (Now 160 a.m., 40 noon, 200 p.m. orally)	0.5 b.d.	Improved	Dryness of mouth, constipation, blurred vision	All much less	None	*Very Good*	190/120–130/90	152/90–120/70	180/120–128/100	124/82–96/60
794	180 b.d. orally	40 b.d. orally	0.5 t.i.d.	Unchanged	Abdominal pain, constipation, blurred vision	Improved	Initial depressive state aggravated	*Poor*	194/120–136/90	188/102–122/60	180/130–130/100	192/132–144/84
795	8 b.d. subcutaneously	8 b.d.	0.5 t.i.d.	Improved	Abdominal pain, distension	Relieved	None	*Good*	220/138–142/92	184/116–114/78	224/142–138/100	174/122–114/90
796	9 b.d. subcutaneously	6 b.d. subcutaneously. Now on 120 b.d. orally	0.5 b.d.	Unchanged (good)	Constipation, abdominal pain, blurred vision	All improved	Depression, somnolence	*Fair*	198/138–156/118	204/130–142/102	190/128–148/98	200/106–124/92
797	240 a.m., 60 noon, 240 p.m. orally	240 b.d. orally	0.5 b.d.	Improved	Blurred vision, hypotensive symptoms	None	None	*Good*	184/130–160/90	184/108–138/82	180/130–140/110	176/100–124/92
902		120 a.m., 80 noon, 120 p.m. orally	0.5 t.i.d.	Good		Impotence		*Good Régime*		164/100–132/94		156/116–118/86
907	600 a.m., 40 noon, 600 p.m. orally	140 a.m., 20 noon, 140 p.m. orally	0.5 t.i.d.	Improved	Dry mouth, constipation	Much less	Diarrhea	*Very Good*	184/126–112/64	176/122–110/74	172/126–104/80	146/104–100/72
909	200 a.m., 80 noon, 200 p.m. orally	200 a.m., 80 noon, 200 p.m. orally	0.5 t.i.d.	Improved	None	None	Shivering	*Good*	206/100–180/110	148/76–112/60	200/150–182/110	142/80–110/60
910		200 a.m., 40 noon, 200 p.m. orally	0.5 b.d.	Satisfactory		Blurred vision	None	*Good Régime*				
912		Up to 440 a.m., 60 noon, 440 p.m.	0.5 b.d.	Very satisfactory		Developed paralytic ileus	None					
		Now 140 a.m., 60 noon, 160 p.m.	0.5 b.d.	Very satisfactory	Minimal on present régime		Very susceptible to cold	*Good Régime*				
916	120 b.d. orally	110 a.m., 40 noon, 120 p.m.	0.5 b.d.	Improved	Blurred vision	Unchanged	None	*Fair*	196/118–138/90	174/100–118/78	190/118–162/118	184/112–132/92
917		60 b.d. orally	0.5 t.i.d.	Satisfactory		Dry mouth		*Good Régime*		154/102–122/80		164/116–120/90
924		40 b.d. orally	0.5 b.d.	Controlled at moderate levels		None	None	*Good Régime*		212/114–160/100		204/112–172/110

the occurrence in three patients of paroxysmal dyspnea of the type described by Winsor.[14] In two of these cases bronchospasm had been previously noted and we attributed their attacks to precipitation of bronchial asthma. In one patient with gallstones the administration of reserpine was followed by typical biliary colic which subsided after the reserpine was withdrawn. In two further patients pain of a similar character occurring after reserpine is under investigation. One patient with chronic ulcerative colitis noted a distinct exacerbation of her symptoms while taking reserpine. Where side effects are prominent within the therapeutic range, small reductions in dosage may appreciably relieve them without sacrificing more than a small part of the hypotensive effect contributed by the reserpine.

The Combination of Pentapyrrolidinium with Reserpine

In table 2 results in 66 cases under treatment with a combination of reserpine and pentapyrrolidinium are presented. A further nine are on a combination of reserpine and hexamethonium. Data showing the extent to which reduction of pentapyrrolidinium or hexamethonium dosage was possible with equally good or better blood pressure control before and after the addition of reserpine is given in 69 cases. The same system of grading results has been used as in the previous report and is based as before on the extent to which therapy with the methonium compound has been improved by the concurrent administration of reserpine. Low doses of the latter were used as shown in the table.

Preparations of pentapyrrolidinium included 4, 5 and 10 per cent solutions in polyvinyl pyrrolidone (P. V. P.), 20 per cent with ephedrine, 0.5 or 1.0 per cent for injection, and a 2 per cent solution and 40 and 200 mg. tablets* for oral use. Preparations of hexamethonium bromide included 10 and 20 per cent solutions in polyvinyl pyrrolidone, 20 per cent, with ephedrine, 0.5 per cent, for injection and hexamethonium bitartrate tablets, each 375 mg., for oral use.

*Ansolysen, May and Baker.

The "Range of Blood Pressure" refers to the highest and lowest readings recorded during a day spent in the clinic. The cases were of all degrees of severity including cases of malignant hypertension. Of the 69 cases, the result of introduction of the combined therapy is now considered very good in 15 cases and good in 20 cases, distinctive benefits having resulted from the addition of reserpine either in an important decrease of side effects or in improvement in the degree of blood pressure control without increase of side effects, or in a combination of these. In 18 the result is classed as fair, some specific advantage having been gained, though this might be of slight degree. Thus, in 53 of the 69 cases the addition of reserpine to the methonium compound in use is considered to have improved the treatment. Sixteen were no better or were worse.

An important advantage from the use of reserpine in combination with pentapyrrolidinium is the extent to which the dose of the latter may be diminished for an equal or greater hypotensive effect on addition of reserpine. Patients stabilized on pentapyrrolidinium usually remark on an increased hypotensive effect from their usual dose within 48 hours of the addition of reserpine. They are warned to expect this and told to reduce the dose of pentapyrrolidinium by progressive decrements (see table 4) until they reach that at which the hypotensive effect at its maximum is tolerable. The severity of parasympathetic side effects is usually reduced proportionally to the fall in methonium dosage. Additionally, in many cases the maximum blood pressure readings permitted by the regimen are significantly lowered. Although the extremes of variation of blood pressure seen with hexamethonium are better controlled with pentapyrrolidinium, some effect of the latter usually still being manifest even 12 hours after the last dose, high peaks may still be encountered. These high (and undoubtedly dangerous) peaks are notably diminished after addition of reserpine.

Side effects from the reserpine are frequent but with the small doses used are seldom a source of serious inconvenience. They have already been detailed in the section on reserpine

TABLE 3.—*Effects on the Blood Pressure and the Incidence of Side Effects of Reserpine and Veratrum*

No.	B. P. range* before reserpine	Dose reserpine (mg.)	B. P. range* after reserpine	Side effects reserpine	Dose veratrum	B. P. after addition veratrum	Side effects veratrum	Definitive form of treatment
25	220/120–190/110	0.5 t.i.d.	185/100–145/80	Negligible. Does not relieve dyspnea completely	2 tabs. Veriloid	210/110–150/90	Nausea and vomiting precluding further elevation of dose	*No*
192		0.5 t.i.d.	180/140–150/110	Negligible	2 tabs. Ver. a.m. 1½ tabs. Ver. noon 2 tabs. Ver. p.m.	170/120–140/100	Nil significant but dyspnea persisted	*No* Better control reserpine—penapyrrolidinium
285	200/120–180/100	0.5 t.i.d.	180/100–160/90	Negligible	2½ tabs. Ver. a.m. 1½ tabs. Ver. noon 2½ tabs. Ver. p.m.	160/100–130/80	Vomiting	*Yes* Continued treatment but on substantially ineffective dose
376	220/140–180/130	3.0 t.i.d.	220/130–210/120	Somnolence	1 tab. Veriloid t.d.s.	220/120–170/80	Not significant at this dosage level	*No* Better control with pentapyrrolidinium
379		2.5 daily	200/130–180/120	Negligible	2½ tabs. Ver. a.m. 1½ tabs. Ver. noon 2½ tabs. Ver. p.m.	190/130–130/90	Vomiting if dose increased above this level	*No* Present regime as detailed with addition of 480 mg. pentapyrrolidinium daily
794	Clinic casual 220/110	0.5 t.i.d.	Clinic casual 190/110	Nasal congestion, coryza, depression	1 tab. Veriloid t.i.d.	Clinic casual 200/100	Vomiting if dose increased above this	*No*
903	220/150–200/130	0.5 t.i.d.	220/130–170/90	Somnolence	2 tabs. Ver. a.m. 1½ tabs. Ver. noon 2 tabs. Ver. p.m.	180/100–130/70	Nausea. Vomiting if dose increased above this	*No* Better control reserpine—pentapyrrolidinium
904	200/120–140/100	0.5 b.d.	210/110–140/100	Negligible	4 mg. mixed alkaloids t.i.d.	140/90 –120/70	Nil significant	*Yes*
910	240/140–220/140	0.5 t.i.d.	220/120–170/110	Negligible	4 tabs. Ver. a.m.	200/110–145/90	Vomiting	*No* Changed to reserpine-pentapyrrolidinium with much better control
912	Casuals before of order 250/150	3.0 t.i.d.	170/100–160/90	Somnolence	2 tabs. Veriloid t.i.d.	190/140–140/90	Vomiting if dose increased above this	*No* Better control reserpine—pentapyrrolidinium

* Range of blood pressure refers to the highest and lowest blood pressure readings recorded during a day spent in the clinic.

alone. Occasionally side effects from reserpine may cancel out those of an opposite character resulting from the ganglionic blocking agents.

The Combination of Reserpine with Veratrum

In 10 cases an extended trial was undertaken of reserpine combined with veratrum. In two of these this mixture is being used as the definitive form of treatment, but in only one has it seemed to give optimum results. In the others the degree of blood pressure control at dose levels at which side effects of the veratrum (nausea and vomiting) were tolerable was inferior to that which could be obtained either with reserpine and pentapyrrolidinium or with the latter alone. The results of the reserpine–veratrum regimen are shown in table 3.

Discussion

Our object in treating hypertensive patients is to reduce the blood pressure to as near normal as possible, for as much of the 24-hour day as can be achieved, and our assessment of the therapeutic value of hypotensive drugs is an assessment of the degree of safe blood pressure reduction which can be obtained without intolerable side effects. We have used these criteria in examining the efficacy of reserpine, alone and in combination with pentapyrrolidinium and with veratrum alkaloids.

Reserpine alone sometimes produces large blood pressure falls but usually only in doses which are accompanied by severe side effects. When smaller doses are used, the side effects are generally less conspicuous, but with such doses we have been able to obtain an adequate hypotensive action in only one-fourth of our patients. Those in whom an adequate control could be achieved by the use of reserpine alone were generally the milder cases, and often, though not invariably, they had low basal blood pressures. Even with the low doses used we have encountered some difficulties from side effects, particularly in the aggravation of symptoms in subjects with bronchial asthma, ulcerative colitis, gallstones and pre-existing mental depression. Further, we have found that in patients with hypertensive heart failure blood pressure reduction by reserpine does not improve breathlessness as with a corresponding reduction by pentapyrrolidinium.

We have examined the effects of combining reserpine with various preparations of veratrum. Our particular interest was to determine whether the addition of reserpine enabled a greater degree of blood pressure reduction to be obtained without the development of vomiting or other side effects of veratrum. The results have been disappointing. In 10 patients the addition of reserpine did not alter the dose of veratrum which led to vomiting, and subtoxic doses of veratrum were not found to exert any distinctively greater hypotensive effect after the addition of reserpine than they did before. We have concluded that the combination of reserpine with veratrum is not a satisfactory means of treating hypertension.

The combination of reserpine with pentapyrrolidinium has also been studied. Pentapyrrolidinium is a substance chemically related to hexamethonium, but, unlike hexamethonium, it can be safely and effectively given by mouth in most patients. It shares with hexamethonium the disadvantage that blockade of the sympathetic ganglia sufficient to induce a useful blood pressure fall cannot usually be obtained without parasympathetic ganglionic blockade also occurring. Although the hypotensive action of pentapyrrolidinium is more prolonged than that of hexamethonium, the blood pressure usually rises to hypertensive levels by the time that the next dose is due to be taken. We have examined the result of combining reserpine with pentapyrrolidinium, with special reference to the incidence of parasympathetic side effects, and also to determine whether the combination of drugs gave a more consistent and smooth hypotensive effect. The results of combining the two drugs have been encouraging. In 53 out of 69 cases in whom the combination was examined, it was possible to produce a better control over the blood pressure with less side effects. In those previously taking pentapyrrolidinium alone, the addition of reserpine made it necessary to reduce the dose of pentapyrrolidinium. In some instances the dose of pentapyrrolidinium required was less than half that previously needed. The greater the reduction in dose of pentapyrrolidinium

the greater was the reduction of side effects due to parasympathetic blockade. In a few it had been difficult to maintain fully effective hypotensive therapy with pentapyrrolidinium alone because of the severity of the side effects, and in these, a striking improvement in the degree of control has usually been obtained by the combination with reserpine.

Over the past four and one-half years we have studied the therapeutic value of the methonium compounds, the veratrum alkaloids, 1-hydrazinophthalazine (Apresoline), the hydrogenated ergot alkaloids, the adrenolytic agents such as Dibenzyline, and reserpine. Of these the combination of reserpine and pentapyrrolidinium appears to be distinctively the most effective means of controlling the blood pressure. Where there is no special urgency about the institution of hypotensive therapy, we now give reserpine in doses of 0.5 mg. thrice daily for a period of about 14 days. No special observation is required during this period since reserpine has the advantage that the dose in the therapeutic range is not immediately critical, in contrast to the extreme accuracy of the dose required when the methonium compounds or the veratrum alkaloids are used. This obviates the need for the close control of dosage so necessary with the latter drugs. In the small dose range, variations in the dose of reserpine of up to 0.5 mg. daily are not accompanied by noticeable variations in the immediate hypotensive effect. At the end of this time a few will be found to have a satisfactorily controlled blood pressure. In our experience these amount to about one in four and are generally the milder cases. In the remainder it is necessary to use pentapyrrolidinium as an additional measure, and this is added under close control. Initial doses and increments of pentapyrrolidinium for oral and parenteral use are shown in table 4. The use of pentapyrrolidinium is described in detail elsewhere.[20, 21] For patients with hypertensive heart failure, or for those with malignant hypertension, reserpine is never adequate alone, and in these patients we commence treatment with pentapyrrolidinium and reserpine in combination.

The duration of treatment with the combination of reserpine and pentapyrrolidinium has been less than six months in all our patients, so that there has been insufficient time to determine whether the long-term effects of treatment will be better than with pentapyrrolidinium alone.

TABLE 4.—*Initial Doses and Dosage Increments of Methonium Compounds*

	Initial dose (mg.)		Dose may be raised or lowered by increments or decrements of (mg.)	
	As salt	As methonium ion	As salt	As methonium ion
Pentapyrrolidinium bitartrate oral....	20	8.9	20	8.9
Pentapyrrolidinium bitartrate "retard" subcutaneous.....	3	1.34	0.5–1.5	0.22–0.67

SUMMARY AND CONCLUSIONS

The clinical use of the alkaloid reserpine in the treatment of hypertension has been studied in 85 hypertensive subjects.

In doses with few side effects, the hypotensive action of reserpine alone produced therapeutically useful falls of blood pressure in 10 out of 40 patients.

The administration of veratrum alkaloids to patients already taking reserpine did not produce any further significant hypotensive effects except in toxic doses.

The administration of reserpine in combination with pentapyrrolidinium to subjects previously taking the latter substance alone, led to an improvement in the hypotensive action, with a reduction in the severity of side effects due to parasympathetic blockade.

It is concluded that the combination of reserpine and pentapyrrolidinium is the most satisfactory means at present available of treating severe hypertension, although some mild hypertensives may be managed with reserpine alone.

SUMMARIO IN INTERLINGUA

Le uso clinic del alcaloide reserpina in le tractamento de hypertension esseva studiate in 85 subjectos hypertensive.

In dosages calculate a producer pauc effectos accessori le action hypotensive de reserpina in

administration isolate se manifestava in 10 inter 40 patientes per un reduction del pression sanguinee a grados therapeuticamente benefic.

Le administration de alcaloides de veratro a patientes jam sub tractamento a reserpina non resultava in ulle significative effectos hypotensive additional, excepte quando illos esseva usate in dosages toxic.

Le administration de reserpina in combination con pentapyrrolidinio a patientes previemente tractate per pentapyrrolidinio isolate resultava in un melioration del action hypotensive con un reduction del severitate de effectos accessori causate per blocage parasympathic.

Nos conclude que le combination de reserpina con pentapyrrolidinio es le plus satisfacente medio nunc disponibile pro le tractamento de hypertension sever. Certe leve casos hypertensive pote esser tractate con reserpina isolate.

Acknowledgments

We wish to thank Messrs. Ciba Ltd., Basle, for generous supplies of reserpine, and Messrs. May & Baker Ltd., Dagenham, England, for supplies of pentapyrrolidinium. We are most grateful to Miss N. Richardson for secretarial assistance.

REFERENCES

[1] Vakil, R. J.: Clinical trial of *Rauwolfia serpentina* in essential hypertension. Brit. Heart J. **11:** 350, 1949.

[2] Müller, J. M., Schlittler, E., and Bein, H. J.: Reserpin, the sedative principle from *Rauwolfia serpentina* Benth. Experientia **8:** 338, 1952.

[3] Bein, H. J.: Zur Pharmakologie des Reserpin, eines neuen Alkaloids aus *Rauwolfia Serpentina* Benth. Experientia **9:** 107, 1953.

[4] —, Gross, F., Tripod, J., and Meier, R.: Experimentelle Untersuchungen über "Serpasil" (Reserpin), ein neues, sehr wirksames Rauwolfiaalkaloid mit neuartiger zentraler Wirkung. Schweiz. med. Wchnschr. **83:** 1007, 1953.

[5] Trapold, J. H., Plummer, A. J., and Yonkman, F. F.: Cardiovascular and respiratory effects of Serpasil, a new crystalline alkaloid from *Rauwolfia serpentina* Benth, in the dog. J. Pharmacol. **110:** 205, 1954.

[6] Plummer, A. J., Earl, A., Schneider, J. A., Trapold, J., and Barrett, W.: Pharmacology of *Rauwolfia* alkaloids, including reserpine. Ann. New York Acad. Sc. **59:** 8, 1954.

[7] McQueen, E. G., Doyle, A. E., and Smirk, F. H.: The circulatory effects of reserpine. Circulation **11:** 161, 1955.

[8] Doyle, A. E., and Smirk, F. H.: Hypotensive action of reserpin. Lancet **1:** 1096, 1954.

[9] Löffler, W., Essellier, A. F., Prott, F., and Wegmann, A.: Hochdruckbehandlung mit einem Rauwolfiaalkaloid (Serpasil). Schweiz. med. Wchnschr. **83:** 1012, 1953.

[10] Wilkins, R. W.: New drug therapies in arterial hypertension. Ann. Int. Med. **37:** 1144, 1952.

[11] —: Clinical usage of *Rauwolfia* alkaloids, including reserpine (Serpasil). Ann. New York Acad. Sc. **59:** 36, 1954.

[12] Freis, E. D., and Ari, R.: Clinical and experimental effects of reserpine in patients with essential hypertension. Ann., New York Acad. Sc. **59:** 45, 1954.

[13] Hafkenschiel, J. H., and Sellers, A. M.: Intravenous reserpine in patients with essential hypertension. Ann. New York Acad. Sc. **59:** 54, 1954.

[14] Winsor, T.: Human pharmacology of reserpine. Ann. New York Acad. Sc. **59:** 61, 1954.

[15] Moyer, J. H.: Cardiovascular and renal hemodynamic response to reserpine (Serpasil), and clinical results of using this agent for the treatment of hypertension. Ann. New York Acad. Sc. **59:** 82, 1954.

[16] Wilkins, R. W., and Judson, W. E.: The use of *Rauwolfia serpentina* in hypertensive patients. New England J. Med. **248:** 48, 1953.

[17] Ford, R. V. and Moyer, J. H.: Preliminary observations of Rauwiloid–hexamethonium combined therapy of hypertension. Am. Heart J. **46:** 754, 1953.

[18] Smirk, F. H., Doyle, A. E., and McQueen, E. G.: Control of blood-pressure by combined action of reserpine and pentapyrrolidinium. Lancet **2:** 159, 1954.

[19] Alam, G. M., and Smirk, F. H.: Casual and basal blood pressures. II. In essential hypertension. Brit. Heart J. **5:** 156, 1943.

[20] Smirk, F. H.: Action of a new methonium compound in arterial hypertension: Pentamethylene 1:5-bis-N-(N-methyl-pyrrolidinium) bitartrate (M. & B. 2050A). Lancet **1:** 457, 1953.

[21] —: Practical details of the treatment of hypertension by hexamethonium salts and by pentamethylene 1:5-bis-N-(N-methyl-pyrrolidinium) bitartrate (M. & B. 2050A). New Zealand M. J. **52:** 325, 1953.

Combined Rauwolfia-Hydralazine Therapy of Hypertensive Patients

By Charles F. Naegele, M.D., Ray H. Rosenman, M.D., Charles L. Hoffman, M.D., and Meyer Friedman, M.D.

Controlled blood pressure responses of 13 hospitalized and 33 ambulatory patients with essential or apparent renal hypertension were studied following combined Rauwolfia-hydralazine therapy. Adequate persistent lowering occurred in most instances of mild or moderate, and frequently even severe, hypertension. Prior and concomitant administration of Rauwolfia largely prevented unpleasant effects of hydralazine, permitted smaller dosage and ease of administration and follow-up —often impossible with large dosage of hydralazine used alone.

DESPITE the present availability of a number of effective hypotensive drugs, none appears to possess the features of the ideal therapeutic depressor agent.[1] An adequate persistent hypotensive response can be induced only in a limited number of patients with the less powerful drugs, and dangerous side effects limit the usefulness of the more powerful depressor agents. Thus, various combinations of such drugs appear to be safer and more effective than any one used alone.[2]

Recently, Wilkins and Judson[3] introduced *Rauwolfia serpentina* into this country, a drug which appears to be a valuable addition to the therapeutic armamentarium available for the treatment of hypertension and its complications. In preliminary studies we have been able generally to confirm their findings concerning the hypotensive and other effects of this drug. Wilkins[1, 2] has suggested that the combination of hydrazinophthalazine (hydralazine) and *Rauwolfia serpentina* appears to be one of the safer depressor combinations, permitting an ease of oral administration and patient follow-up not possible with various other combinations of hypotensive agents. The present study is concerned with determining the clinical usefulness of this particular combination of drugs in the routine treatment of both hospitalized and office patients with hypertension.

From the Medical Service, United States Public Health Service Hospital, and the Harold Brunn Institute, Mount Zion Hospital, San Francisco, Calif.

Material and Methods

The patients who comprised this study, with few exceptions, had moderate or severe hypertension, usually diagnosed as "essential" hypertension, but in some instances as "renal." There were no cases of "malignant" hypertension, as usually considered. The patients were divided into two series.

The first series consisted of 13 merchant seamen with known persistent severe hypertension for periods of time ranging from at least 6 months to over 10 years. These men had been previously under both outpatient and inpatient medical care. All patients were hospitalized for the purpose of this study and their hypertensive state carefully reevaluated under routine hospital conditions, while ambulatory and at bed rest. The patients were permitted ambulatory status on the ward while under observation. Each patient had a complete history and physical examination and laboratory studies which included complete blood counts and determination of the sedimentation rate, urinalysis and stain of the urinary sediment for "Sternheimer cells,"[4] renal concentration and dilution tests, determination of nonprotein nitrogen, fractional phenolsulfonphthalein test, chest x-ray examination and cardiac fluoroscopy, intravenous pyelography, electrocardiogram and ballistocardiogram. Observations of blood pressure and pulse rate were recorded at least twice daily under standardized conditions, and general symptomatology was noted at each of these periods. There were four instances of apparent "renal" hypertension associated with chronic pyelonephritis.

After usually four or more weeks of control observation, the patients were given *Rauwolfia serpentina*,* 4 mg. per day by mouth. After one week,

* Rauwiloid (Riker Laboratories, Inc., Los Angeles). The doses of *Rauwolfia serpentina* are expressed in terms of alkaloids of the alseroxylon fraction (Rauwiloid, Riker).

hydrazinophthalazine (hydralazine) was added in initial oral dosage of 75 mg. daily, and rapidly increased up to 600 mg. daily given in four divided doses. Observations then were continued for three to seven weeks.

The second series consisted of 33 unselected ambulatory office patients with known persistent hypertension for from six months to 23 years. Seven of these were believed to represent "renal" hypertension. Hypertension occurred in three of these for the first time during toxemia of pregnancy. The hypertension in the remaining four cases appeared to be initiated by a chronic pyelonephritis. In addition to history and complete physical examination, laboratory studies included complete blood counts and determination of sedimentation rate, cardiac fluoroscopy, electrocardiography and ballistocardiography, urinalysis and examination of urine sediment with the Sternheimer stain. Where indicated, renal dilution-concentration tests and intravenous pyelography were performed, and in many instances the blood pressure response to Regitine was tested. During the control observation and treatment periods, blood pressures and pulse rates were obtained in the recumbent position in the afternoon, initially at weekly and, later, usually at monthly intervals. In many instances the patients had been previously observed in private practice over a period of one to five years or during the previous 12-month period while under treatment with hydralazine alone and/or hexamethonium.

At the beginning of the present study other drugs were withdrawn and *Rauwolfia serpentina** was administered orally in a total daily dosage of 4 to 8 mg. After one week to three months, hydralazine was added in 27 instances, in initial daily dosage of 75 mg. and, where necessary, rapidly increased up to a total of 300 mg. daily, except in four patients who received a somewhat larger dosage. The patients subsequently were observed for 3 to 12 months.

Results

Table 1 depicts the blood pressure responses of the hospitalized group of nine patients with essential hypertension. The blood pressures were taken twice daily and recorded on a graph. The control values listed in table 1 represent the highest, lowest and approximate median blood pressure observed during the initial period of observation. Each patient of this series had severe hypertension, generally of known or obviously long-standing duration. The recorded blood pressures after therapy represent the approximate median blood pressures, as well as the highest and lowest levels recorded during the last 10 days of the therapeutic trial period. When response to therapy was observed, the blood pressures usually fell rapidly and remained stabilized at their lowered levels with only minor fluctuations and an occasional transient rise of greater magnitude. No significant response occurred in case 1 or case 9 despite 600 mg. daily dosage of hydralazine, although the highest and lowest diastolic values were somewhat diminished in case 9. Both of these patients exhibited severe hypertensive cardiovascular disease, with a failure of the blood pressure to fall during the preliminary control period of bed rest. Each of the other patients also exhibited severe chronic hypertension, but some reduction of blood pressure occurred in each instance during therapy. The fall in blood pressure observed in cases 3 and 8 might have been more marked had larger dosage of hy-

TABLE 1.—*Effect of Rauwolfia-Hydralazine in Hospitalized Patients with "Essential" Hypertension*

Case	Pt.	Age	Control Observation				Observation on Rauwolfia-Hydralazine Therapy*				
			Duration (wks.)	Blood Press. (mm. Hg)			Duration (wks.)	Dosage of Hydralazine (mg./day)	Blood Press. (mm. Hg)		
				Median	High	Low			Median	High	Low
1.	OL	49	4	224/124	230/160	180/100	4	600	220/120	230/130	180/110
2.	JW	53	5	190/120	230/140	180/110	4	500	140/85	160/100	130/70
3.	CD	40	4	165/115	180/120	150/90	4	200	150/100	160/110	140/80
4.	HC	57	4	200/115	220/130	170/110	4	350	160/90	190/100	140/85
5.	MC	49	2	170/100	200/130	150/90	4	600	150/90	185/100	140/60
6.	JD	54	3	170/116	205/120	160/110	4	400	140/90	150/100	130/70
7.	DL	24	5	190/140	230/140	180/110	4	600	170/90	180/130	160/80
8.	JS	55	2	190/120	200/130	180/110	3	300	170/98	180/110	150/90
9.	JS	38	2	180/110	210/160	170/130	7	600	180/107	195/110	160/90

* Last 10 days of therapy.

TABLE 2.—*Effect of Rauwolfia and Hydralazine in Hospitalized Patients with "Renal" Hypertension*

Case	Pt.	Age	Control Observation				Observation on Rauwolfia-Hydralazine Therapy*				
			Duration (wks.)	Blood Press. (mm. Hg)			Duration (wks.)	Dosage of Hydralazine (mg./day)	Blood Press. (mm. Hg)		
				Median	High	Low			Median	High	Low
1.	AW	49	4	220/130	230/150	200/110	7	600	220/110	230/140	200/105
2.	CR	62	4	220/120	260/160	190/110	5	600	220/120	250/160	190/110
3.	AL	58	4	200/110	260/130	175/105	4	600	210/108	230/120	185/100
4.	AB	61	3	160/90	180/120	140/80	4		130/70	150/75	110/60

* Last 10 days of therapy.

dralazine been employed. Some reduction of the resting pulse rates occurred in every case, but this effect was not marked, perhaps because the pretreatment values were already lowered secondary to prolonged bed rest during the preliminary control period of observations.

Table 2 shows the blood pressure responses of the four hospitalized patients with hypertension occurring in association with chronic pyelonephritis. This diagnosis was based upon a history of pyelonephritis and/or the findings of persistent albuminuria, pyuria and urinary Sternheimer "motility" cells[4] in the urine. Although none of these patients exhibited azotemia, diminished renal function was present in most. Each patient had a severe hypertension and, except in case 4, it was fixed at a level not altered by the preliminary period of bed rest. In the patient whose blood pressure fell during bed rest alone (case 4), therapy with Rauwolfia alone further depressed the blood pressure to normotensive levels. In the other three cases, satisfactory lowering of the blood pressure could not be induced even by daily dosage of 600 mg. of hydralazine.

Table 3 presents the blood pressures observed in the 26 ambulatory office patients with essential hypertension. Less significance can be attached to these observations and to the recorded blood pressures since the blood pressures were obtained under necessarily variable circumstances and at intervals varying up to one month. The values listed in the table represent the *final* blood pressures obtained during the control and, posttreatment periods. During the treatment period of the ambulatory patients, the dosage of hydralazine was adjusted in an attempt to achieve or to maintain satisfactory blood pressure reductions. In some instances this required later increase of dosage, and on occasion the daily dosage could be reduced. As a result some variation of the blood pressure was observed. The blood pressure values in tables 3 and 4 represent the final values observed during therapy with the recorded dosage of hydralazine. In general, these patients exhibited less severe hypertension than those in the hos-

TABLE 3.—*Effects of Rauwolfia and Hydralazine in Twenty-Six Ambulatory Patients with Essential Hypertension*

Case	Pt.	Age	Sex	Known Duration Hypertension (yrs.)	Final Pretreatment Blood Press. (mm. Hg)	Observation on Treatment with Rauwolfia and Hydralazine		
						Duration (mos.)	Dosage Hydralazine (mg./day)	Final Blood Press. (mm. Hg)
1.	IA	54	M	9	230/120	12	150	150/85
2.	EB	73	F	4	200/130	12		170/104
3.	BB	38	M	2	170/120	12	250	150/80
4.	SC	61	F	1	200/130	12	300	140/85
5.	MD	44	F	5	210/130	10	150	130/85
6.	HF	56	M	10	210/110	12	150	130/70
7.	JH	42	M	15	210/150	12	150	150/100
8.	JJ	60	M	4	190/100	5	75	155/80
9.	AK	54	F		210/105	3	150	150/90
10.	RL	53	M		170/120	10	150	140/90
11.	DL	51	F	5	200/130	12	300	150/90
12.	OM	57	M		160/110	11	250	150/95
13.	HM	62	F		210/106	5		150/84
14.	AR	45	M	4	220/120	9	150	150/90
15.	MS	46	F	10	220/112	9	250	160/88
16.	JT	48	M	23	180/130	12	250	150/90
17.	AV	66	M		200/130	4	75	185/90
18.	GW	58	F		190/110	12	200	155/85
19.	SW	57	F	8	210/110	12	300	170/85
20.	LP	34	F	16	190/134	3	75	150/100
21.	AS	63	F	3	220/120	3		180/90
22.	FF	58	M	10	170/104	6		130/84
23.	ME	29	M	9(labile)	180/94	4		140/80
24.	HB	38	F	4	180/115	4		145/95
25.	JB	39	M	15	180/130	9	600	150/110
26.	MF	53	F	4	270/140	6	400	130/75

TABLE 4.—*Effects of Rauwolfia and Hydralazine in Patients with Apparent "Renal" Hypertension*

Case	Pt.	Age	Sex	Known Duration Hypertension (yrs.)	Final Pretreatment Blood Press. (mm. Hg)	Observations on Treatment with Rauwolfia and Hydralazine		
						Duration (mos.)	Dosage Hydralazine (mg./day)	Final Blood Press. (mm. Hg)
1.	CB	43	F	½	200/110	12	150	145/85
2.	HD	60	M	9	240/140	12	550	160/90
3.	MM	57	M	3	210/105	12		160/85
4.	MM	45	F	14	170/100	12	150	120/80
5.	NN	37	F	20	210/140	12	250	140/95
6.	JR	63	M		220/130	12	400	200/110
7.	JW	56	M		160/105	12		120/80

pitalized group, and a smaller dosage of Rauwolfia and of hydralazine was employed with few exceptions. Some blood pressure reduction occurred in every case. Six patients received only Rauwolfia, which lowered the blood pressure to normotensive levels in three patients (cases 13, 22, 23), and almost to normal in one (case 24). In another instance, (case 21), the diastolic pressure fell to normal, and the systolic remained elevated, possibly because of advanced sclerotic changes in the aorta. No hydralazine was given to case 2 because of the presence of advanced coronary artery disease. A reduction of the blood pressure to normal levels (150 systolic, 90 diastolic) occurred in many of the remaining patients on combined therapy. The blood pressure response was not entirely satisfactory in three patients (cases 7, 20, 25). Each of these patients had severe hypertension, known to be present for many years. Side effects prevented administration of a larger and perhaps more effective dosage of hydralazine in case 7 and case 20.

The effects of combined therapy in the ambulatory series of seven patients with "renal" hypertension are presented in table 4. This diagnosis was based on the fact that hypertension either began with a toxemia of pregnancy or was present in association with apparent chronic pyelonephritis, based on the criteria described for the hospitalized group. Hypertension began in cases 1, 4, and 5 with toxemia of pregnancy, but severe hypertension was observed only recently in cases 1 and 4. It is of interest that therapy was effective in these two patients, but was less effective despite a larger dosage of hydralazine in case 5 where severe, fixed hypertension, known for many years, had failed to respond to a sympathectomy performed five years ago. The remaining patients presented evidence of chronic pyelonephritis. The results of therapy were excellent in case 2 and Raulwolfia alone served to reduce the blood pressure effectively in cases 3 and 7. Patient 6 had only a fair result, which was not improved by further increasing the dosage of hydralazine.

A reduction of the pulse rate, often to bradycardic levels, occurred in many of the ambulatory groups of patients. Nasal congestion was observed in some of the patients but was troublesome in only one instance. Significant increase of bowel frequency occurred in one patient who had a history of "irritable colon" syndrome. No serious side effects occurred in any patient, although increased angina was observed in one instance, preventing a larger and probably more effective dosage of hydralazine. In contrast to an earlier experience with hydralazine used alone, it was observed that the prior administration of Rauwolfia markedly reduced the incidence and severity of palpitation, tachycardia, and "headache" commonly observed when initiating treatment with hydralazine, and permitted administration of the latter in an initial dosage of 25 to 50 mg. given three times daily. Finally, although precise comparative studies were not performed in this group of patients, it is our definite impression that the concomitant administration of Rauwolfia and hydralazine induces a degree of blood pressure reduction which would require substantially larger doses of hydralazine if used alone, doses more prone to induce serious side effects and more difficult to control. We have also been impressed with the favorable effects of Rauwolfia upon the anxiety, general tension and other symptoms prone to occur in hypertensive patients.

DISCUSSION

Rauwolfia serpentina has been used in India for over 10 years in the treatment of hypertension.[5, 8] Wilkins and Judson (3) introduced the drug into the United States and found that it had a mild hypotensive effect, caused

bradycardia frequently, and had a sedative effect occasionally, but did not result in postural hypotension or vagal stimulation. They observed that it was well tolerated by hypertensive patients over prolonged periods, with hypotensive effects slow both to appear and to disappear. Wilkins[1, 2] has suggested that rauwolfia is most useful as an adjunct to more powerful hypotensive agents. The logical use of Rauwolfia in conjunction with other hypotensive agents[2] led to this study of combined Rauwolfia and hydralazine therapy in an attempt to determine the clinical usefulness of this drug combination. Our results with this combination of drugs confirm in general those previously presented by Wilkins and Judson.[3] Thus, in a small series of hospitalized patients followed carefully over relatively long periods of time, control of hypertension was achieved in those with mild or moderate, and occasionally severe hypertension. Failures occurred in some patients with long-standing, fixed, sev ere hypertension, or those with apparent "renal" hypertension. This experience was confirmed in a larger number of unselected ambulatory office patients with hypertension.

In the dosage used, side effects attributable to Rauwolfia were significantly few and included only bradycardia, observed frequently, nasal congestion, and a sedative effect observed infrequently. The prior administration of Rauwolfia appeared to prevent the commonly encountered headache, tachycardia, and palpitation which frequently occur when initiating therapy with hydralazine, and permitted initial hydralazine therapy in moderate dosage. Moreover, concomitant administration of Rauwolfia appeared to permit effective therapy with hydralazine in significantly smaller dosage of the latter, doses which avoid the more serious side effects of hydralazine administration which can occur with large doses given over long periods.[9, 10] Finally, the safety and ease of administration of this combination of drugs permitted an ease of patient follow-up which, following stabilization, required only bimonthly or monthly routine check. Thus, combined Rauwolfia-hydralazine therapy appears to us to be a preferable combination of drugs for most patients with hypertension who fail to respond to Rauwolfia used alone, although other drug combinations have been shown to be advantageous.[11] As shown by Wilkins,[1-3] the substitution or addition of a third hypotensive agent may be required to control the blood pressure of selected patients with severe, chronic, fixed hypertension or "renal" hypertension.

Summary

Blood pressure responses of 33 ambulatory and 13 hospitalized patients with hypertension were studied under controlled conditions during combined therapy with *Rauwolfia serpentina* and hydralazine. Adequate lowering of the blood pressure was achieved in most patients with mild or moderate hypertension, and frequently in those with severe hypertension. With the dosage used in this study, an inadequate response occurred only in patients with severe, chronic, fixed hypertension or with hypertension of apparent renal origin.

Prior administration of Rauwolfia largely prevented untoward effects prone to occur when initiating therapy with hydralazine, and permitted initial administration of hydralazine in larger dosage than ordinarily tolerated. With combined Rauwolfia-hydralazine therapy, adequate lowering of the blood pressure was achieved in a high incidence, using moderate dosage of hydralazine which permitted an ease of administration and patient follow-up often not possible with larger dosage of hydralazine used alone.

Summario in Interlingua

Le reactiones del pression sanguinee a un therapia combinate de *Rauwolfia serpentina* e hydralazina esseva studiate sub conditiones contrclate in 46 patientes hypertensive inter le quales 13 esseva hospitalisate e 33 ambulatori. Satisfacente reductiones del pression sanguinee esseva effectuate in le majoritate del patientes con leve o moderate hypertension e frequentemente etiam in patientes con hypertension sever. Le dosages usate in iste studio resultava in reactiones inadequate solo in patientes con sever e chronic hypertension fixate o in patientes con hypertension de origine apparentemente renal.

Le pre-administration de rauwolfia preveniva in grande mesura le effectos nocive que occurre facilemente quando le therapia es comenciate per le administration de hydralazina. Iste pre-administration de rauwolfia etiam rendeva possibile un administration initial de hydralazina in dosages plus grande que illos normalmente tolerate. Le therapia combinate de rauwolfia e hydralazina resultava in un adequate reduction del pression sanguinee in un alte procentage del casos ben que le dosages usate esseva satis moderate pro evitar omne difficultates in le administration del drogas e le supervigilantia posterior del patiente, lo que es frequentemente impossibile quando on usa plus grande dosages de hydralazina isolate.

ACKNOWLEDGMENT

We wish to express our appreciation to Dr. Norman W. Karr of the Riker Laboratories, Inc., Los Angeles, for the generous supplies of Rauwiloid, the preparation of *Rauwolfia serpentina* used in this study.

REFERENCES

[1] WILKINS, R. W.: New drug therapies in arterial hypertension. Ann. Int. Med., **37:** 1144, 1952.

[2] —: Combinations of drugs in the treatment of essential hypertension. Mississippi Doctor **30:** 350, 1953.

[3] —, AND JUDSON, W. E.: The use of *Rauwolfia serpentina* in hypertensive patients. New England J. Med. **248:** 48, 1953.

[4] STERNHEIMER, R., AND MALBIN, B.: Clinical recognition of pyelonephritis with a new stain for urinary sediments. Am. J. Med. **11:** 312, 1951.

[5] BHATIA, B. B.: On use of *Rauwolfia serpentina* in high blood pressure. J. Indian M. A. **11:** 262, 1942.

[6] GUPTA, J. C., DEB, A. K., AND KAHALI, B. S.: Preliminary observations on use of *Rauwolfia serpentina* benth. in treatment of mental disorders. Indian M. Gaz. **78:** 547, 1943.

[7] VAKIL, R. J.: Clinical trial of *Rauwolfia serpentina* in essential hypertension. Brit. Heart J. **2:** 350, 1949.

[8] CHAKRAVERTY, N. K., CHAUDURI, RAI, CHANDURI, M. N. AND R. N.: *Rauwolfia serpentina* in essential hypertension. Indian M. Gaz. **86:** 348 1951.

[9] MORROW, J. J., SCHROEDER, H. A., PERRY JR., H. M.: Studies on the control of hypertension by Hyphex. II. Toxic Reactions. Circulation **8:** 829, 1953.

[10] DUSTAN, H. P., TAYLOR, R. D., CORCORAN, A. C., AND PAGE, I. H.: Rheumatic and febrile syndrome during prolonged hydralazine treatment. J. A. M. A. **154:** 23, 1954.

[11] FORD, R. V., AND MEYER, J. H.: Preliminary observations of Rauwiloid-hexamethonium combined therapy of hypertension. Am. Heart J. **46:** 754, 1953.

Cardiovascular Actions of Sodium Nitroprusside in Animals and Hypertensive Patients

By Irvine H. Page, A. C. Corcoran, H. P. Dustan and Theodore Koppanyi

Certain chemical and pharmacological properties of sodium nitroprusside, a cheap, readily available chemical, have been described. It is a powerful hypotensive agent when given intravenously to hypertensive patients. It is no more effective than the sodium thiocyanate into which it is converted when given by mouth. Prolonged infusion has proved highly effective in the treatment of hypertensive encephalopathy.

THE EXPERIENCE of most physicians with sodium nitroprusside ($Na_2[Fe(CN)_5(NO)]\cdot 2H_2O$) is limited to its use in diagnostic tests for acetone, aldehydes, alkali sulfides and sulfur dioxide. It has been used in suicides only rarely, and curiously, only by medical and nursing personnel[1]; the proximate cause of death was believed to be cyanogen (prusside) formed by decomposition of nitroprusside (=$Fe(CN)_5NO$). Hypodermically, the average lethal dose of nitroprusside in guinea pigs is 7.5 mg. and that of potassium cyanide is 1.9 mg.[2]

The hypotensive action of parenteral nitroprusside has been given little attention other than by Johnson[3] who described it as being 50 to 1000 times greater than that of the nitrite ion. He estimated the ratio between depressor and toxic dosages as 1:10. Its depressor effect resembled that of sodium nitrite in that it seemed to be due to decreased peripheral vascular resistance and was independent of innervation. Johnson did not believe the evidence supported the assertion that toxic effects of parenteral nitroprusside could be due to liberation of cyanogen.

This report includes additional data on the biochemistry and pharmacology of nitroprusside, as well as an evaluation of its place in the treatment of hypertensive disease.

From the Research Division of the Cleveland Clinic Foundation, and the Frank E. Bunts Educational Institute, Cleveland, Ohio and the Department of Pharmacology, Georgetown University School of Medicine, Washington, D. C.

Biochemical Reactions

Nitroprusside decomposes with liberation of cyanogen when placed in contact with animal tissues.[4] It reacts similarly when mixed with protein-free filtrates of blood, and this over a wide range of pH, so the reaction is not enzymatic.

Since the depressor action of nitroprusside might be associated with decomposition, this process was studied further by Dr. Merlin Bumpus of the Research Division of the Cleveland Clinic. The iron atom in nitroprusside is in the ferrous state and as well as cobalt is able to form complexes with sulfhydryl-containing amino acids.[5] From this it seemed likely that the reaction depends on the interaction of sulfhydryl compounds in body fluids with the nitroprusside ion. This view was tested by incubating, in the manner described by Hill,[4] aliquots of a solution of sodium nitroprusside with blood and with solutions of glycine, proline, methionine and cysteine. Neither glycine nor proline caused cyanogen to be liberated; some was detected in the methionine incubate and the cysteine incubate gave an amount which corresponded to that recovered from the mixture with blood.

This reaction was also examined by Dr. Carlos Monge C., who compared the release of cyanogen from nitroprusside mixed with blood versus plasma, measuring cyanogen by the method of Gettler and Goldbaum.[6] In one experiment, for example, nitroprusside was added to fresh heparinized human plasma in a concentration of 5 micrograms per ml.; the

mixture was incubated for 60 minutes at 38 C., during which time no release of cyanogen could be demonstrated. An equal volume of red cells was then added to the plasma and the incubation continued; the cyanogen released per milliliter of the original plasma was found to be about 0.6 micrograms at 45 minutes and 2.6 at the end of two hours. The latter yield is substantially complete. Incubation of nitroprusside with whole blood at 38 C. yielded complete recovery as cyanogen at about 90 minutes; recoveries at 10, 30, 50 and 70 minutes were respectively approximately 6, 50, 75, and 90 per cent complete.

These observations suggest that decomposition of nitroprusside in contact with blood or tissue is attributable to interaction of its iron atom with sulfhydryl groups; the activity of whole blood in this regard may be due to the rich sulfhydryl content of red blood cells. The delay in completing the reaction observed in incubated mixtures of blood or red cells with nitroprusside probably reflects the time required for contact of the nitroprusside with the intracellular sulfhydryl groups. The fact that this reaction is completed only after a delay, while the depressor response to nitroprusside is quick in onset and short lasting, indicates that decomposition is not essential to the depressor activity.

Liberation of cyanogen from nitroprusside results *in vivo* in formation of thiocyanate; this conversion[7] is apparently enzymatic and dependent on the hepatic enzyme "rhodanase". Prolonged administration of nitroprusside, therefore, results in the accumulation of thiocyanate in blood. Thiocyanate is oxidized to cyanide[8] by a thiocyanate oxidase contained in erythrocytes.[9]

A series of compounds containing N or NO (cyanide, ferrocyanide, ferricyanide, nitrite, nitrosomethylurea and hydroxylamine) was tested for depressor activity in anesthetized dogs. The amounts given corresponded in nitrogen or NO content to that of a depressor dose of sodium nitroprusside. Among these only nitrite showed any depressor action. These observations point to the Fe-NO grouping in nitroprusside (=$Fe(CN)_5NO$) as the active depressor.

Pharmacology of Sodium Nitroprusside

Effect on Arterial Pressure of Normal Animals

The usual dose given to dogs anesthetized with pentobarbital was 2.5 micrograms per kilogram intravenously. The average fall in arterial pressure in 20 animals was 57 mm. Hg with a range of −20 to −80 mm. Hg. Heart rate and respiration were little changed unless the hypotension was severe when slight tachycardia occurred. Quite as often the heart rate slowed after nitroprusside. No rhythm change was noted. Repeated administration did not lead to tachyphylaxis nor to refractoriness when given at intervals of about 10 minutes.

Intravenous infusions of nitroprusside permitted blood pressure to be maintained almost indefinitely at any desired level by altering inflow rate. In the presence of hypotension elicited by infusion of nitroprusside, responses to a variety of intravenously injected vasoactive substances (noradrenaline, 1,1-dimethyl-4-phenylpiperazinium iodide—DMPP—vasopressin) were moderately depressed.

Effect Under Various Experimental Conditions. Operative procedures were performed aseptically and sufficient time was allowed before tests for recovery and healing. Few of the conditions imposed had any striking effects on the hypotensive action of nitroprusside. Hemispherectomy moderately increased the depressor response, dorsal nerve root section from C-8 to the cauda equina, ablation of the carotid sinuses or cardiac denervation were without effect. Ganglionectomy from T-1 to T-9 was ineffective, but "total" surgical sympathectomy increased depressor responsiveness.

Adrenergic blocking agents such as Dibenamine (20 mg. per kilogram) or benzodioxane did not prevent the depressor action of nitroprusside. In contrast, administration of 15 to 30 per cent carbon dioxide by inhalation under curare markedly diminished the response.

Establishment of Eck fistulas or ligations of the hepatic artery or both had no convincing effect on nitroprusside response. Bilateral adrenalectomy had no effect in the first few hours after operation.

Denervated kidneys were perfused by a

constant output pump either from the same animal or from a donor. Nitroprusside injected in amounts of 0.25 to 1.22 mg. into the arterial perfusion circuit caused moderate vasodilatation. The fall in pressure in the donor animal which the nitroprusside produced after renal perfusion was usually greater than that in the perfusion circuit. For example, 0.25 mg. caused a fall of −16 mm. Hg in the renal circuit but −70 mm. Hg in the donor. Perfusion of the denervated dog's hind leg by Dr. James McCubbin showed that nitroprusside in doses of 0.25 mg. caused severe and prolonged vasodilatation.

Augmentation of Depressor Response. Autonomic ganglion blockade by tetraethylammonium chloride (10 to 15 mg. per kilogram) or hexamethonium (3 mg. per kilogram) markedly augmented the depressor response to nitroprusside (table 1). Hydralazine (2 to 3 mg. per kilogram) also elicited moderate augmentation after about 15 to 25 minutes. Single injections of the depressor drug alstonine hydrochloride (1 mg. per kilogram) had no effect but when infused (125 mg. in 100 ml. salt solution) nitroprusside depressor action was moderately augmented. Veriloid (a mixture of veratrum alkaloids) (0.08 mg. per kilogram) given intravenously appeared to reduce it slightly during the period of hypotension.

Miscellaneous Observations. An infusion of sodium thiosulfate did not block the depressor action of nitroprusside. Atropine and vagotomy were without effect on its hypotensive action. Nitroprusside in markedly hypotensive doses produced no relaxation of the virgin or pregnant uterus of rabbits or of the duodenum of dogs.

Renal Effects

A. *Dogs.* Nitroprusside was infused into normal dogs, conscious or anesthetized with pentobarbital, in dogs with experimental renal hypertension and in one dog with chronic neurogenic hypertension due to buffer nerve section, during measurements of the plasma clearances of para-aminohippurate at low plasma concentration (C_{PAH}) and of exogenous creatinine (C_{CR}). Arterial pressure (Pm) was recorded from a mercury manometer connected to a femoral artery; maximal tubular excretory capacity for para-aminohippurate was determined in two normal dogs and maximal tubular reabsorptive capacity for glucose in another two. These observations were made over three to five control periods of about 10 minutes each and, 10 minutes after beginning nitroprusside infusion, over similar lengths of time. The data are summarized in table 2.

TABLE 1.—*Examples of Augmentation of Depressor action of Nitroprusside in Anesthetized Dogs*

	Control Blood Pressure	Blood Pressure Change	Time
Sodium nitroprusside 50 micrograms	120	−10	10:15
Hydralazine 2 mg/Kg	120	0	10:25
Nitroprusside 50 micrograms	116	−14	10:29
Nitroprusside 50 micrograms	122	−30	11:49
Sodium nitroprusside 50 micrograms	108	−26	1:40
Hydralazine 3 mg/Kg	110	0	1:52
Nitroprusside 50 micrograms	120	−36	2:02
Nitroprusside 50 micrograms	120	−60	2:15
Nitroprusside 50 micrograms	108	−56	2:30
Sodium nitroprusside 50 gamma	146	−24	10:25
	150	−24	10:31
TEAC 5 mg/Kg	146	+10–22	10:50
TEAC 5 mg/Kg	140	+34–10	11:01
Nitroprusside 50 micrograms	134	−66	11:07
Nitroprusside 50 micrograms	134	−46	11:12

In normal dogs, nitroprusside caused a slight increase in the clearance of para-aminohippurate, no change in clearance of creatinine, a slight reduction in arterial pressure and, assuming para-aminohippurate clearance at low plasma concentrations to equal renal plasma flow, a decrease in renal vascular resistance (R). In the doses used, it had no effects on maximal tubular excretory capacity for para-amino hippurate or maximal tubular reabsorptive capacity for glucose. Mean doses in the group were 7.9 micrograms per kilogram of body weight per minute; doubling the dose above this level, especially at the start of the nitroprusside infusion, usually resulted in retching and vomiting.

In dogs with renal hypertension, the doses

TABLE 2.—*Effect of Nitroprusside Infusion on Renal Functions in Dogs*

No.	Group	Dosage	Ratios of Test to Control				T_{mPAH}	T_{mG}	Duration in minutes
			C_{PAH}	C_{Cr}	Pm	R			
1	Normal	4.0	1.13	1.00	0.87	0.71			27
2*	Normal	4.3†	1.26	1.19	0.96	0.78			85
3*	Normal	5.9†	1.06	0.79	0.83	0.81			61
4*	Normal	6.8	1.74	1.36	0.80	0.46			31
5	Normal	7.0		0.91	0.68		0.96		30
6	Normal	8.8	1.01	0.80	0.82	0.75			17
		16.0	0.93	0.85	0.85	0.81			20
7	Normal	10.0	1.13	0.90	0.65	0.56		0.97	32
8*	Normal	10.0		0.96	0.82		0.99		30
9	Normal	15.0	0.01	0.91	0.77	0.76		1.08	32
Mean.....	Normal	(7.9)	(1.19)	(0.98)	(0.80)	(0.69)			
10*	Renal	15.6	1.12	0.76	0.92	0.82			30
11*	Renal	22	0.92	0.69	0.76	0.82			40
12	Renal	30	0.76	0.47	0.67	0.90			27
13*	Renal	25	0.88	0.76	0.89	0.92			37
Mean.....		(23)	(0.94)	(0.67)	(0.81)	(0.87)			
14	Neurog.	8	1.05	0.78	0.47	0.42			20

* Experiments indicated by an asterisk were done on dogs anesthetized with pentobarbital.

Dosage is indicated in micrograms per Kg. body weight per minute.

Ratios are means of observations during test periods divided by means of observations in control.

Duration indicates the period of time during the observations that were in test periods.

† Dosages indicated by a dagger are means of varied doses; in experiment 3, dosage was increased stepwise from 1 to 9 and in experiment 3 from *e* to 13 micrograms.

Experiment 6 includes observations during 2 periods of urine collection at the lower dose and 2 subsequent periods at the higher dosage.

C_{PAH} = plasma clearance of *p*-aminohippurate, C_{CR} = plasma clearance of exogenous creatinine, Pm = arterial pressure and R = renal vascular resistance calculated as $Pm\text{-}5/C_{PAH}$.

averaged 23 micrograms per kilogram per minute. Clearance of para-aminohippurate was not increased in the group by nitroprusside infusion. Clearance of creatinine was more depressed than in normal dogs, arterial pressure was equally decreased and renal vascular resistance less depressed than in the normal group. In the dog with experimental neurogenic hypertension, the dosage used was about equal to the mean of that used in normal dogs, and the effects on clearances of para-aminohippurate and creatinine were similar; this dog showed very large decreases in arterial pressure and renal resistance during administration of nitroprusside.

In brief, the data demonstrate that infusions of nitroprusside in small amounts cause moderate decreases in arterial pressure in normal and renal hypertensive dogs; the degree of renal vasodilatation elicited by the infusion seems greater in normal dogs in which the decrease in vascular resistance exceeds that of mean pressure, while in renal hypertensive dogs, these two functions decrease proportionately. Further, the renal hypertensive dogs manifest a consistent decrease in creatinine clearance during the infusion; this is a result of an increased "afferent" resistance not removed by nitroprusside and may be due to compression of the kidney by the perinephritic hull. The heightened responsiveness of the arterial pressure and renal vascular resistance of the dog with neurogenic hypertension to nitroprusside corresponds with the sensitivity of such dogs to some other vasodepressor drugs.[10]

B. *Patients.* Nitroprusside was given by

TABLE 3.—*Effect of Nitroprusside on Renal Functions in Patients with Hypertensive Disease*

No.	Control Pm. mm. Hg	Control R.B.F. cc/min.	Ratios of Test to Control			
			C_{PAH}	GFR × 1.1	Pm	R
1	165	740	1.27	1.13	0.84	0.65
2	161	664	1.01	0.98	0.89	0.89
3a	145	502	0.97	0.83	0.90	0.93
b	138	507	0.93	0.98	0.90	0.96
4	130	498	1.01	0.76	0.91	0.90
5	166	370	1.03	1.01	0.83	0.80
6	149	265	0.93	0.84	0.89	0.92
7a	175	252	0.83	0.83	0.91	1.03
b	151	90	1.09	1.08	0.87	0.81
Mean			(1.01)	(0.93)	(0.88)	(0.88)

Data collected as in table 1 and arranged in order of decreasing renal function.

Pm = systolic and diastolic arterial pressure/2.

RBF = renal blood flow cc per 1.73 sq. m. per min. calculated as C_{PAH}/l hematocrit.

GFR = plasma mannitol clearance multiplied by 1.1.

Control values are means of observations in 3 control periods of about 10 minutes duration each.

infusion in dosages of 60 to 100 micrograms per minute during observations of renal functions (para-aminohippurate and mannitol clearances), in patients with hypertensive disease. These studies were conducted by Dr. William Wagner. The data obtained in nine series of observations of arterial pressure, para-aminohippurate clearance and glomerular filtration rate (estimated as mannitol clearance × 1.1) are summarized in table 3 in order of decreasing control levels of estimated renal blood flow (C_{PAH}/l-hematocrit).

The observations indicate that nitroprusside in the dosages used is moderately vasodepressor and induces renal vasodilatation which is roughly equivalent to the decrease of pressure. It does not increase para-aminohippurate clearance and, in this respect the data accord with those from dogs with renal hypertension. However, the dosage used is less on a weight basis and the tendency to decreased glomerular filtration during nitroprusside hypotension less marked.

Chronic Administration to Neurogenic and Renal Hypertensive Dogs

One renal hypertensive dog prepared by Page's method and one neurogenic hypertensive by Grimson's debuffering technique were fed nitroprusside in capsules for six months (60 to 420 mg. per day) to keep the serum level of thiocyanate at an average of 4 mg. per 100 ml. Arterial pressure fell from an average of 222 mm. Hg to 202 mm. Hg in the renal hypertensive dog; this change is probably not significant. Neither was there a significant change in the neurogenic hypertensive's blood pressure. Amounts of potassium thiocyanate sufficient to give comparable levels in the blood also failed to lower arterial pressure. With both nitroprusside and thiocyanate, the doses were surprisingly large as compared with those required to maintain similar thiocyanate concentrations in the blood of patients.

Chronic Administration to Rats

Groups of six adult male and six female rats received an intravenous injection of 1 mg. per kilogram of nitroprusside five times a week for one year and 12 others were offered as their only water supply 0.1 per cent solution of nitroprusside for the same length of time. The animals maintained their weight and showed no abnormalities, gross or microscopic, in the liver or kidneys.

Chronic Oral Administration of Nitroprusside to Patients

Nitroprusside was administered for from six weeks to two years to 16 hypertensive patients, most of whom had been intensively studied for long periods before the drug was used. Nine of these had malignant, and the remainder, severe essential hypertension.

The initial dose by mouth was usually 30 mg. four times a day and increased to 60 mg. four times a day after a few days. The thiocyanate level in the blood was a guide to dosage: from 8 to 12 mg. per 100 ml. was considered satisfactory. An example of the relationship between dosage and thiocyanate level in a patient with good renal function is given in table 4. Patients with reduced renal function often

TABLE 4.—*Relationship of Nitroprusside Dosage and Thiocyanate Serum Level in a Patient with Essential Hypertension and Normal Clearance**

Date	Dosage mg. Q.I.D.	Serum Thiocyanate level mg/100 ml.
4/21/52	30	—
4/28	60	2.8
5/2	120	5.2
5/9	120	10.8
5/15	60–120	11.6
5/23	60–120	13.0
5/29	60–120	13.9
6/5	60–120	11.0
6/12	60–120	16.8
6/17	60–120	16.2
6/20	0	
6/26	0	9.4
7/23	30	
8/14	30	6.8
8/21	60	8.3
8/25	30–60	9.4
9/4	30–60	8.4
9/10	240	10.7
9/17		8.6
9/25	210	9.8
10/2	210	11.4
10/9	210	11.6
10/16	210	12.0
10/23	210	11.0
10/30	180	10.6
11/6	180	10.3
11/20	180	14.7
12/11	180	10.2
12/23	210	10.5
1/22/53	210	12.0
2/5		12.1
2/12	210	14.3
3/5	180	10.2
3/26	210	
4/9/53	210	—
5/7	180	13.0
6/11	180	8.1
6/25	210	12.0
7/9	180	
7/22	180	11.7
8/20	180	10.6
9/4	Stroke and death	

* No significant effect on blood pressure. The clearance remained normal throughout. Heart enlarged to 150% of normal.

showed a more rapid and prolonged rise in thiocyanate.

Signs and symptoms of toxicity closely resembled those following administration of potassium thiocyanate. Fatigue, nausea, loss of appetite, and weakness were the most common symptoms shown by most patients; other patients ran almost the entire gamut of symptoms, just as they do with thiocyanate. On two occasions, skin rashes due to thiocyanate required discontinuance of the drug. Headache associated with hypertensive disease often disappeared following nitroprusside but in two patients it became worse. Anemia may have been augmented in a few patients with renal failure but this is hard to prove in a disease characterized by anemia.

The effect on average arterial pressure after about six weeks administration was usually to cause a moderate (>20/15 mm. Hg) decrease. Decreases of this degree occurred in nine of 16 patients, and in those with malignant as well as essential hypertension; greater but transient decreases of arterial pressure were occasionally observed. In the remainder, the drug had no provable effect, even when administered for over a year. Nitroprusside placebo was used either before or after the drug itself. Often several months were required for the blood pressure to return to the control level on discontinuing the drug; on its return thiocyanate was given instead of nitroprusside to increase serum level of thiocyanate to that observed during administration of nitroprusside. A typical example is shown in fig. 1, in which it will be seen that the blood pressure fell about equally with both drugs. We have been unable to distinguish between the fall in blood pressure elicited by nitroprusside and thiocyanate.

The drug seems to have no definite effect over a period of months on renal blood flow or filtration rate. It is very difficult to be sure whether nitroprusside aided in healing the lesions of malignant hypertension in the eyegrounds. In two patients they cleared during treatment with nitroprusside. It certainly does not prevent the appearance of heart failure, myocardial infarction, or stroke, although it might retard their appearance.

Since hydralazine and hexamethonium given to normal anesthetized dogs augment the depressor action of nitroprusside given intravenously, we tried a combination of the drugs in patients. We have been unable to prove any true synergism when the combinations were given by mouth.

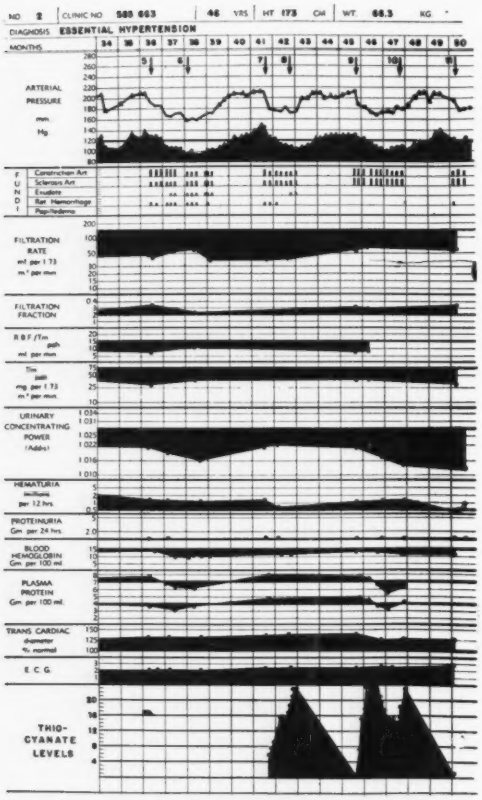


FIG. 1. Cardiovascular-renal effects of sodium nitroprusside and sodium thiocyanate in a patient with essential hypertension. Each dot on the arterial pressure chart represents an average of measurements taken morning and evening for a week. At (5) nitroprusside was given by mouth and stopped at (6). Again it was started at (7) and stopped at (8). Sodium thiocyanate was started at (9) and stopped at (10). The blood thiocyanate level was about equal after nitroprusside and thiocyanate with about equal reduction of arterial pressure.

Sensitivity to Intravenous Nitroprusside of Hypertensive Patients

The effects of intravenous nitroprusside were explored in six patients in the malignant phase of essential hypertension, two with severe essential hypertension, one with hypertension secondary to unilateral pyelonephritis, and one with malignant hypertension associated with polycystic renal disease. The purpose was to determine the sensitivity of hypertensive patients, to define the reproducibility of the responses elicited and to investigate the effects on sensitivity to intravenous nitroprusside of chronic oral administration of hydralazine. The study was carried out by Dr. William Wagner. Nitroprusside was given by the constant infusion of a solution made up from a one per cent stock solution which had been prepared for use by passage through a Seitz filter. The rate of infusion was regulated by a tunnel clamp so as to deliver amounts ranging from 20 to 200 micrograms per minute.

Nitroprusside had a hypotensive effect in all patients (table 5a). Five patients showed a reproducible response to the same amounts of nitroprusside in repeated control studies; in three, marked variability of response to the same infusion rates was noted. Two normotensive adult women who received doses of 300 and 500 micrograms per minute had somewhat varying blood pressure responses. In one, a fall in diastolic pressure from 88 to 52 mm. Hg was associated with a decrease in systolic pressure from 128 to 76 mm. Hg while in the other the diastolic pressure fell from 76 to 36 mm. Hg but the systolic pressure was main-

TABLE 5a.—*Hypotensive Effect of Intravenous Nitroprusside in Hypertensive Patients*

Patient	Blood Pressure in mm. Hg		Nitroprusside gamma/min.
	Control	Test	
1	218/160	−64/50	120
2	266/160	−116/52	120
3	210/128	−42/32	60
4	228/156	−86/64	140
5	210/140	−60/30	200

b. *Effect of Hydralazine on Nitroprusside Response*

Patient	Study Period	Blood Pressure in mm. Hg		Nitroprusside gamma/min.
		Control	Test	
6	control	186/128	−32/28	200
	Apresoline	190/130	−38/30	60
7	control	208/126	−28/14	60
	Apresoline	212/132	−56/48	60
8	control	224/136	−60/36	200
	Apresoline	235/131	−73/41	120
9	control	240/140	−72/38	120
	Apresoline	210/120	−44/30	120
10	control	188/110	−28/10	60
	Apresoline	210/120	−30/20	60

TABLE 6.—*Nitroprusside Infusions for Complication of Malignant Hypertension*

Indication	No. of Infusions	Duration	Control B.P.	B.P. Reduction range	Nitroprusside/min. range
A.V.D.	1	12 hr/day–15 days	210/152	30/40–85/82	40–115
C.V.A.	1	8–24 hrs.–8 days	262/162	−20/12–−112/92	35–125
C.V.A.	1	5 hrs.	224/180	−24/30	50–70
A.V.D.	1	2 days	230/158	−60/28	25–70
N.H.	1	2 days	234/136	−54/20–−82/38	25–225
A.V.D.	1	14 days	247/153	−47/33–−127/77	150–330
Enceph.	5	10 hr.–7 days	300/200–	−20/15–	80–380
P.O.	1		240/142	−144/120	
P.O.	2	20 hr.–4 days	210/160–192/140	80/70	15–500

Abbreviations:
A.V.D. = advancing vascular disease
C.V.A. = cerebral hemorrhage
N.H. = severe nasal hemorrhage
Enceph. = encephalopathy
P.O. = postoperative intracranial IX nerve section.

tained at approximately 100 mm. Hg. In both, the pulse rate increased 30 beats per minute; intense nasal stuffiness occurred in one. Comparing of the response of these normotensives with that of the hypertensives, the latter seem much more sensitive to the hypotensive effect of nitroprusside.

The effect on responsiveness to chronic oral hydralazine treatment (table 5) was investigated in five; tests were done before and during the administration of therapeutic amounts (400 to 800 mg. per day) of this drug. Three patients showed reproducible increases in sensitivity to intravenous nitroprusside while taking hydralazine in a dose which was not of itself depressor.

Treatment of Hypertensive Encephalopathy

The hypotensive effects of intravenous nitroprusside have been used in the control of some of the complications of hypertensive vascular disease (table 6). For this purpose constant infusions were continued for periods ranging from five hours to fourteen days (fig. 2). Prolonged decreases of arterial pressure could be maintained by regulation of the rate of infusion; tolerance to nitroprusside was observed in only one patient; this was overcome by giving intravenously a dose of hexamethonium which did not of itself decrease arterial pressure. The prolonged administration of nitroprusside was without deleterious

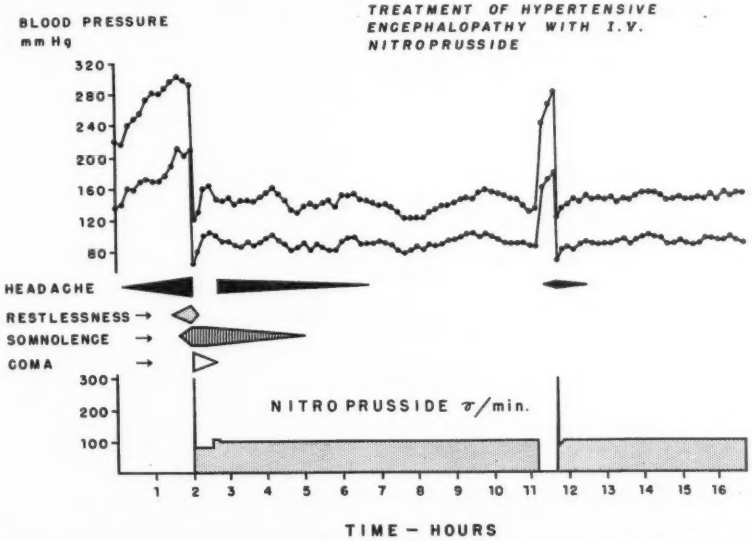


FIG. 2. Treatment of hypertensive encephalopathy with intravenous infusion of sodium nitroprusside. The patient was first somnolent, then comatose. The upper third shows the effect on arterial pressure, the middle, signs and symptoms, and lower third, the amount of nitroprusside in micrograms per minute.

effect; in one patient who had severe renal insufficiency, treatment was discontinued after 14 days because the serum thiocyanate level had risen to 12.6 mg. per 100 cc. Administration from a constant infusion pump enables excellent control of blood pressure at stable levels for many hours once an optimum rate of infusion has been established.

The effectiveness of nitroprusside is best exemplified by its use in five bouts of hypertensive encephalopathy in one patient. The following is a brief description of one of these episodes.

Case history: I. G., a 29 year old colored woman with severe hypertensive vascular disease had sudden onset of generalized headache which awoke her from a sound sleep. She was given 0.25 Gm. sodium amytal intramuscularly without effect. The headache became increasingly severe; restlessness and drowsiness developed. Upon examination she appeared acutely ill; her face was very pale. Although drowsy she responded fairly well to questioning. A neurological examination revealed no localizing signs and the blood pressure was 290/170. On the basis of these findings it seemed that she had rapidly progressing hypertensive encephalopathy. Several hours previously she had received 100 mg. of hexamethonium intravenously without change in supine blood pressure readings and only slight postural hypotension which had disappeared within a few hours. Accordingly, intravenous nitroprusside was given. As a solution of 100 micrograms per ml. was being prepared she became semicomatose; the restlessness increased. Just as the venipuncture was made she ceased to respond to painful stimuli. The nitroprusside was given rapidly at approximately 300 micrograms per minute; within one minute the blood pressure had fallen to 120/70 so the infusion rate was decreased to 100 micrograms per minute. As the blood pressure fell the restlessness disappeared promptly. Within 15 to 20 minutes after start of the infusion, she began to respond to painful stimuli; the level of consciousness gradually improved and within one hour she was responding to questioning but was drowsy and complained of a severe headache. With only occasional and minor adjustments, the infusion rate was maintained at 100 micrograms per minute for a period of 30 hours and the blood pressure ranged from 200/100 to 140/90. The headache and drowsiness continued for several hours but slowly disappeared. She became alert and cheerful about 24 hours after the beginning of the infusion; the nitroprusside infusion rate was gradually decreased during the next few hours; the blood pressure rose and when the infusion was discontinued, reached levels of around 210/130. The headache did not recur.

Discussion

Nitroprusside has been shown to decompose in contact with tissue with liberation of cyanogen. This is probably dependent on the interaction of the sulfhydryl compounds in body fluids with the nitroprusside ion. But this reaction is so slow as to preclude its being responsible for the hypotensive effect. The intact nitroprusside molecule itself must be the cause of the quick depression of arterial pressure when it is injected intravenously. Chronic administration by mouth has no such intense hypotensive action; rather its effect seems to be due to the increase in the thiocyanate level of the blood into which the cyanogen is converted. In hypertensive patients, the effects of nitroprusside and thiocyanate, given by mouth over periods of months, are indistinguishable.

Nitroprusside is an unusually powerful hypotensive agent acting in doses of 2 micrograms per kilogram in anesthetized dogs. Unanesthetized hypertensive patients required about 50 to 100 micrograms per minute to elicit sustained hypotension. The drug seems to act primarily on the vascular musculature relatively independently of the nervous system. Its depressor action is augmented in both dogs and patients by autonomic ganglion blocking agents such as tetraethylammonium chloride (TEAC) and hexamethonium, as well as moderately by such drugs as hydralazine and alstonine. We presume this is due chiefly to damping of the buffer reflexes.

The kidney blood vessels are responsive to nitroprusside. Nitroprusside infusions in normal dogs cause relatively more renal vasodilation than decrease in arterial pressure. In dogs with renal hypertension (produced by Page's method) somewhat larger doses elicit equivalent decreases in renal resistance and arterial pressure, which are often associated with decreased rate of glomerular filtration. In hypertensive patients renal vasodilatation is roughly proportional to the decrease in arterial pressure, and glomerular filtration is not disproportionately decreased by the fall in pressure.

Since the substance was so powerful in reduc-

ng blood pressure when given intravenously, ve have tested it carefully in both hypertensive logs and man for its activity when given by nouth. Dogs with both experimental renal and neurogenic hypertension given large doses for periods up to six months failed to show an impressive effect on blood pressure. These animals proved surprisingly resistant to elevation of their blood thiocyanate level; much greater doses of both nitroprusside and thiocyanate were required than in hypertensive human beings. Rats given large amounts of nitroprusside for a year showed no tissue changes at autopsy.

Clinical trial of nitroprusside for periods up to two years demonstrated no superiority of nitroprusside over thiocyanate. In fact, they seem identical in both their therapeutic and toxic actions.

The results of sensitivity tests, using nitroprusside infusions, suggest that hypertensive patients are more sensitive than the two normotensive subjects we have studied. The sensitivity to intravenous nitroprusside could be increased by chronic administration of hydralazine or hexamethonium.

The drug proved to be of very considerable practical use in the treatment of patients with hypertensive encephalopathy. Both signs and symptoms disappeared dramatically and rapidly when the arterial pressure was reduced to approximately normal levels by its constant infusion. Since no tachyphylaxis occurred, it was not necessary steadily to increase the dosage over a period of days. Since nitroprusside is cheap, readily available and the infusions easy to prepare and stable, it has seemed to us to have much to recommend it for hypertensive crises, and our experiences in its use shows this to be true.

Summary

1. Cyanogen is liberated from mixtures of sodium nitroprusside and blood or cysteine or methionine. The decomposition of nitroprusside by blood or tissues is attributable to interaction of its ion with sulfhydryl groups. This decomposition of the nitroprusside ion is not necessary for its cardiovascular action.

2. Intravenously injected nitroprusside is strongly hypotensive without producing tachyphylaxis. Adrenergic blocking agents and surgical ablation of portions of the central nervous system failed to abolish its action. Autonomic ganglion blocking agents markedly augment the hypotensive response; hydralazine and alstonine do so moderately. Dogs with experimental neurogenic hypertension are more sensitive than renal hypertensive or normotensive dogs to the depressor effect of intravenous nitroprusside.

3. Nitroprusside is moderately vasodilator in perfused kidneys of dogs and strongly dilator in perfused hind legs. In normal conscious dogs it caused slight increase in renal blood flow and decrease in vascular resistance with no effect on the maximal tubular excretory capacity for para-aminohippurate (Tm_{PAH}) OR the maximal tubular capacity for reabsorption of glucose (Tm_G), when infused intravenously. A dog with neurogenic hypertension in contrast with those with renal hypertension, exhibited large decreases in both arterial pressure and renal resistance.

4. Moderately depressor doses induce renal vasodilatation in hypertensive patients which is roughly equivalent to the decrease of pressure. It does not increase renal blood flow appreciably nor decrease glomerular filtration conspicuously.

5. Chronic oral administration of nitroprusside to renal and neurogenic hypertensive dogs produced no significant change in arterial pressure. Enough sodium thiocyanate to give thiocyanate blood levels comparable to those obtained with nitroprusside was also ineffective. Nitroprusside produced no tissue changes in rats given 1 mg. per kilogram intravenously five times a week for a year.

6. Patients with arterial hypertension have been treated with oral nitroprusside for periods up to two years, using the thiocyanate level as a guide to dosage. The effects are identical with those observed when comparable blood levels of thiocyanate are induced by oral administration of sodium thiocyanate. True synergism with hydralazine or hexamethonium has not been proved when nitroprusside was given by mouth.

7. Hypertensive patients are more sensitive

to the hypotensive action of intravenously administered nitroprusside than normotensive subjects. Chronic treatment with hydralazine or hexamethonium or single doses seems to increase this sensitivity.

8. Constant infusion of nitroprusside into patients with hypertensive encephalopathy has kept the arterial pressure at normal levels as long as 14 days with complete disappearance of the signs and symptoms. No deleterious effects from such prolonged administration have been noted and the rapidity of its therapeutic effects has been striking.

SUMMARIO IN INTERLINGUA

Es describite certe qualitates chimic e pharmacologic de nitroprussiato de natrium. Iste droga es non-costose e facilemente obtenibile. Illo es un potente hypotensor quando administrate intravenosemente a patientes hypertensive. Illo non es plus efficace que le thiocyanato de natrium que se forma ex illo in le administration oral. Le prolongate infusion de nitroprussiato de natrium se ha provate multo efficace in le tractamento de encephalopathia hypertensive.

REFERENCES

[1] LAZARUS-BARLOW, P., AND NORMAN, G. M.: Fatal cases of poisoning with sodium nitroprusside. Brit. M. J., **1:** 407, 1941.

[2] MAHAFFEY, L. W.: A contribution to the toxicology of sodium nitroprusside. 2. Toxicity of sodium nitroprusside for guinea pigs. Australian Chem. Inst. J. and Proc., **9:** 93, 1942.

[3] JOHNSON, C. C.: The actions and toxicity of sodium nitroprusside. Arch. Internat. Pharmacodynamie, **35:** 480, 1929.

[4] HILLS, H. E.: A contribution to the toxicology of sodium nitroprusside. 1. The decomposition and determination of sodium nitroprusside. Australian Chem. Inst. J. and Proc., **9:** 89, 1942.

[5] MICHAELIS, L.: Oxidation reduction systems of biological significance; mechanism of catalytic effect of iron on oxidation of cysteine. J. Biol. Chem., **84:** 777, 1929.

[6] GETTLER, A. O., AND GOLDBAUM L.: Detection and estimation of microquantities of cyanide. Analyt. Chem., **19:** 270, 1947.

[7] LANG, K.: Die Rhodanbildung im Tierkorper. Biochem. Z., **259:** 243, 1933.

[8] PINES, K. L., AND CRYMBLE, M. M.: In vitro conversion of thiocyanate to cyanide in the presence of erythrocytes. Proc. Soc. Exp. Biol. Med., **81:** 160, 1952.

[9] GOLDSTEIN, F., AND RIEDER, F.: Conversion of thiocyanate to cyanide by an erythrocytic enzyme. Am. J. Physiol., **173:** 287, 1953.

[10] PAGE, I. H.: "Neural and humoral control of blood vessels", in Ciba Foundation Symposium on Hypertension, Humoral and Neurogenic factors. London, J. & A. Churchill, 1954.

Experimental Bacterial Endocarditis Due to Streptococcus Mitis

I. Method of Induction

By Robert A. Rabens, M.D., Joseph E. Geraci, M.D., John H. Grindlay, M.D., and Alfred G. Karlson, Ph.D.

It is important in order to advance the increasingly successful attack on subacute bacterial endocarditis to be able to produce the disease experimentally and to treat it with new and improved therapeutic regimens. Since endocarditis caused by *Streptococcus mitis* has not been consistently produced previously in the dog, a study was undertaken in which cardiovascular stress was created by the establishment of aortico-inferior vena caval and bilateral iliofemoral arteriovenous shunts. After a period of antibacterial treatment and of stabilization, daily intravenous injections of broth cultures of *S. mitis* were begun. In 50 per cent of 24 animals bacterial endocarditis developed, simulating that found in clinical cases at necropsy. These animals had widely patent fistulas and 11 showed evidences of congestive heart failure. Of the remaining 12 animals, five with patent fistulas died of the effects of multiple infected pulmonary emboli. Seven others whose shunts had closed were killed and found to have no significant lesions other than healed caval infections.

THE evaluation of new treatment regimens for bacterial endocarditis would be greatly facilitated by the development of a simple method of producing the disease in animals. In the past most of the methods employed in the production of experimental endocarditis involved one major approach; that is, the intravenous injection of organisms into the animal, either with or without preceding injury to one or several of the heart valves. More recently, attempts have been made to increase the cardiac work load by various procedures followed by the injection of organisms. Although positive results were sometimes obtained by each of these procedures, *Streptococcus mitis* endocarditis in the dog has not been consistently produced.

The purpose of this paper is to present our experience with the production of bacterial endocarditis with a culture of a penicillin-sensitive *Streptococcus mitis* isolated from a human case of subacute bacterial endocarditis. Utilizing the method of Lillehei and his co-workers,[1, 2] aorto-inferior vena caval anastomoses were created in dogs followed by intravenous injections of the organism.

Materials and Methods

1. Preparation of Animals.—Twenty-four mature, healthy, vaccinated (antidistemper) dogs were used.* In 22 animals an aorto-inferior vena caval shunt was prepared by making a side-to-side anastomosis of 10 to 12 mm. between the lower part of the aorta and the inferior vena cava just above their bifurcations.† A strip of ivalon plastic sponge about 2 mm. in diameter was wrapped around the anastomotic site. A distinct thrill was palpated, and a marked whorling of arterialized blood was visualized in the vena cava immediately after the proximal arterial clamp was removed. In two animals a two-stage operation was done with the construction of bilateral iliac and femoral shunts each 12 mm. in length.

On the day of the operation and continuing for four consecutive days, the animals were given an intramuscular injection of penicillin (200,000 units) and dihydrostreptomycin (0.3 Gm.) to prevent bacteremia from postoperative wound infection and to eradicate any organisms which may have already been present. After a lapse of two days to permit

Abridgment of portion of thesis submitted by Dr. Rabens to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Medicine. The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

* Nine other animals were not included owing to premature deaths of seven and closure of the fistula shortly after operation in two others.

† We are indebted to Drs. J. M. Janes and R. Thors for the creation of the majority of the fistulas.

TABLE 1.—*Arteriovenous Fistula Plus Bacteremia: 24 Animals*

Group	Animals	Blood Cultures	Major Cause of Death	Contributory Cause of Death
I. With bacterial endocarditis	12			
A. With active endocarditis	11	Consistently positive	Congestive heart failure	Embolic complications, pneumonia
B. With healed endocarditis	1	Consistently positive, then negative for final 6 weeks	Killed	
II. Without bacterial endocarditis	12			
A. With fatal septicemia	5	Consistently positive	Septicemia	Pulmonary infarction, pneumonia
B. With stenotic fistulas	7	Positive, then negative for final 6 weeks	Killed	

excretion of the antibiotics, blood cultures were made on three successive days followed by two days of observation. The blood cultures, which were negative, were done to insure that no bacteremia existed before the experimental infection was started. This 12-day preinfection period served as a stabilization phase in which many of the more important physiologic changes occurring as a result of the stress imposed by the fistula took place.

2. Administration of Organisms.—On the twelfth postoperative day, 6 ml. of blood were obtained for culture from the jugular vein of each animal. With the needle in place, an immediate injection was then given of a whole 24-hour dextrose-brain broth culture of *Streptococcus mitis*. This procedure was repeated for at least 14 consecutive days in the 15 animals whose daily blood cultures remained positive for the streptococcus. Blood cultures were made every other day thereafter in these animals. In the case of the nine animals whose blood cultures remained negative or were only occasionally positive, the daily 10 ml. injections of culture were continued for periods of up to 36 days. Five animals were given additional injections consisting of two daily injections of 10 ml. of whole culture for 11 to 20 days followed by three daily doses of 20 ml. for 14 to 17 days. In only two of these five animals was bacteremia established.

3. Clinical Examinations.—A daily examination was made just prior to the drawing of blood for cultures and the injection of bacteria. This was done in order to determine the effects of the surgical procedure and also to determine the onset and course of the endocarditis. The examination included the following: daily weights, rectal temperatures, auscultation of the heart and lungs, auscultation and palpation of the abdominal and inguinal regions for bruits and thrills and inspection of the body for edema, evidences of collateral circulation and petechiae.

4. Termination of Experiment.—In 11 animals signs of endocarditis developed and all 11 died from congestive heart failure and the complications incident to their endocarditis. One additional animal with healed endocarditis was killed.* Of the remaining 12, 5 had a consistent bacteremia and died from the effects of their septicemia and of widespread pulmonary embolism. The other seven were killed* after having negative blood cultures for at least six weeks. A necropsy was carried out on every animal. Small portions of valvular and caval vegetations (opposite the site of anastomosis) were cultured on blood agar and in dextrose brain broth. Smears of these areas were stained with Gram's stain.†

For purposes of comparison, the animals were divided into two groups (table) depending on the presence (group I) or the absence (group II) of endocarditis as determined at necropsy. Each group was further divided into two subgroups: those that died of their induced disease (A) and those that were killed (B).

RESULTS

1. Clinical Findings.—It was found that the diagnosis of bacterial endocarditis was not difficult to make once the process was well established. However, the exact time of the onset of the disease was difficult to ascertain. This was true for several reasons: (1) cardiac murmurs, systolic in time, were present shortly after the surgical procedure, (2) bacteremia due to *S. mitis* usually occurred after several days of injections, and (3) transient hyperthermia occurred as a result of the bacteremia alone.

In all animals, regardless of the eventual development of endocarditis, there was a soft,

* The animals were killed with a barbiturate given intravenously.

† Gross and histopathologic studies have been made on the various organs from each animal. The results will be reported in a separate communication.

apical systolic murmur appearing shortly after the operation. For several weeks after operation significant tachycardia (120 to 200 beats per minute) and an increase in the intensity of both heart tones were noted in all animals. The Nicoldoni or Branham sign was positive for the life of the animals whose fistulas remained widely patent.

In animals of group IA (11 animals with active endocarditis) there was a close correlation between the clinical signs and the necropsy findings in six of eight animals with aortic valvulitis. These animals had loud grade 2 to 4 (basis of 1 to 4) basal systolic murmurs followed by softer early diastolic murmurs at the base. In the remaining five animals with active endocarditis a softer systolic apical murmur of grade 2 intensity was heard. The single animal of group IB (healed endocarditis) had no significant murmurs. In the group without endocarditis (group IIA and B) there were, nevertheless, signs of cardiac stress such as soft, apical systolic murmurs graded 1 in all 12 animals in the postoperative period. These murmurs persisted in seven animals. At necropsy, cardiac dilatation and predominantly left ventricular hypertrophy were noted in animals of this group.

Thus, the onset of definite, loud precordial murmurs, more persistently elevated temperature and consistently positive blood cultures signaled the presence of bacterial endocarditis. The time between the initial injection and the probable onset of infection of the heart was variable, the onset of infection occurring 7 to 70 days after the injections commenced (average 18 days). Blood cultures became positive in 1 to 11 days (average 4.4 days) and remained so for the duration of the life of these animals. These animals lived from 7 to 128 days (average 41.7 days), once the diagnosis was established.

The single animal with healed endocarditis was not suspected of having bacterial endocarditis despite the presence of promptly and persistently positive blood cultures for five months. This animal was killed six weeks after the cultures became negative, some 202 days after the onset of injections.

In 12 animals endocarditis did not develop. Of the 5 animals that died of septicemia and of pulmonary infarction (group IIA), four died 46 to 58 days after the first injections (average 48.5 days). The clinical diagnosis of endocarditis was not considered in these animals, although in one, a persistent to-and-fro, grade 1 apical murmur was heard. The fifth animal died from the effects of a ruptured cerebral mycotic aneurysm 184 days after the injections were started. In all of these five, the blood cultures became positive in 7 to 24 days and remained positive. The remaining seven animals (group IIB) had healed, scarred caval lesions, closed or markedly stenotic arteriovenous fistulas and no endocarditis. These animals presented a variable intermittent bacteremia which finally cleared completely. They were killed 86 to 213 days (average 135 days) after initial injections. Two of these seven were remarkable because of the persistence of positive blood cultures for five and six months respectively, finally presenting a sterile blood stream for the final six weeks.

Auscultation of the abdomen and groin proved to be a decided diagnostic aid. The loudness of the bruit depended on the size of the fistula, the distance of the latter from the stethoscope and the presence or absence of local intravascular lesions. A loud systolic bruit graded 3 to 4 (basis 1 to 4) and a distinct thrill which persisted until death were found in animals with a patent shunt (17 animals, comprising all of groups I and IIA). On the other hand, a gradually decreasing bruit and thrill, especially when coupled with subsidence of peripheral edema and collateral venous circulation, pointed, in the seven animals of group IIB, to functional and anatomic closure of the fistula.

Daily weight records showed a gradual loss of weight through the terminal period of congestive heart failure in infected animals. The animals with active endocarditis (group IA) lost an average of 16.4 per cent of their body weight. The five animals dying of pulmonary infarction and sepsis (group IIA) had a comparable loss of 15.7 per cent of body weight. Of the seven animals of group IIB, three gained weight, two others lost an average of only 6.9 per cent of their body weight and in two the

weight remained constant. The general physical appearance of the animals with valvulitis was not significantly different from that of other animals until late in the course of the infection. Then, marked anorexia, listlessness, dyspnea, orthopnea and unsteadiness of gait accompanied the development of effusions, moist pulmonary rales, progressive dependent edema, distention of the veins and weakened and irregular heart tones. Daily rectal temperatures were found to be most consistently elevated in the animals with endocarditis, but this tendency was not pronounced or maintained until the final few weeks of life. The induced bacteremia caused a transient fever. Terminally, temperatures ranging from 102.5 to 105 F. were the rule in animals with bacterial endocarditis. Definite evidence of splenomegaly and of embolic phenomena was searched for but not found.

2. Bacteriologic Observations.—Positive blood cultures for *S. mitis* were obtained during and following the period of injections, but persistently positive cultures were seen only in those animals with a localized infected lesion. Such lesions included the vegetations in the inferior vena cava and on the heart valves.

In the 12 animals with bacterial endocarditis the blood cultures became positive in 1 to 11 days after injections were started. Heavily positive cultures (11 to innumerable colonies per plate) were obtained in animals with endocarditis, especially during the final two weeks of life. In one animal with healed endocarditis positive blood cultures developed after the first injection and the cultures remained positive for five months, finally reverting to negative for the six weeks before the animal was killed. One other animal required supplemental injections of 20 cc. thrice per day to initiate bacteremia occurring after five days of these injections.

Group IIA consisted of five animals in which endocarditis did not develop. In all these animals blood cultures became persistently positive after 7 to 24 injections and remained positive until death. These animals had friable vegetations at the site of the fistula and widespread areas of infarction of the lungs. One of these five animals required additional injections of 10 ml. twice per day for 20 days and 20 ml. thrice per day for 17 days before blood cultures became consistently positive. This animal died from a ruptured cerebral mycotic aneurysm six months after the first injection. Group IIB consisted of seven animals that presented healed, scarred caval lesions with closed or markedly stenotic arteriovenous fistulas and no evidence of bacterial endocarditis. These animals had extremely variable intermittent bacteremia of a mild nature (1 to 10 colonies per plate) and were killed on an average of three months after the beginning of injections. Three of these seven received supplemental injections in a vain effort to infect the blood stream.

The organism was demonstrated in postmortem specimens by stain and by culture. Smears were made of lesions in 10 of the 11 hearts with active endocarditis and all had gram-positive, short-chained cocci as the only organism present. Cultures from these vegetations yielded *S. mitis* in all. The cultures of the vena caval vegetations revealed *S. mitis* in 16 of the 17 animals with patent fistulas

Comment

Observations on endocarditis in man by Abbott[3] showed that usually a damaged valve or an arteriovenous shunt and bacteremia are necessary for the development of bacterial endocarditis. Circulating bacteria seem to have a selective affinity for the slightly damaged, insufficient valve and for the endothelial surface that is traumatized by a vigorous blood impact. Illustrative examples are the endocarditis involving mild aortic or mitral insufficiency, the endocarditis associated with a ventricular septal defect and the endarteritis resulting from a patent ductus arteriosus or a peripheral arteriovenous fistula. In this study, the lesions of the inferior vena cava are examples of infection due to trauma caused by increased blood flow. Traumatic arteriovenous fistulas and aneurysm are a rare cause of bacterial endocarditis and endarteritis in man. Rienhoff and Hamman,[4] Williams[5] and Cutler and Wolf[6] have reported such cases. The latter authors emphasized the sclerotic thickening of the free edges of the aortic cusps in aortic in-

sufficiency as a substrate for endocarditis. Allen[7, 8] studied human hearts affected by subacute bacterial endocarditis. He was impressed by the constancy of the location of the vegetations on the outflow surface of the valve and especially at the lines of closure. The idea was presented that hemic impact and contact factors are operative in this disease. These factors may explain the localization of valvular and vascular lesions observed in the present study.

In a review of experimental bacterial endocarditis those studies which utilize the principle of cardiovascular stress are pertinent to this discussion. Nedzel[9] injected Pitressin and streptococci intravenously, producing a proliferative valvulitis. The drug was thought to increase the cardiac work and the force of valve closure, causing a bland endocarditic lesion on which bacteria were deposited. However, Visscher and Henschel,[10] using epinephrine and Pitressin and the intravenous injection of bacteria, were unable to confirm this work. Highman and Altland[11] found that intermittent exposure of rats to low pressure simulating a 25,000-foot altitude yielded thickened valves in nearly all of the animals, and fibrinous vegetations in 35 per cent of the group. These workers[12] subjected a group of rats to similar environmental conditions for four hours a day for 30 or more days, following which the rats received massive single injections of streptococci from human cases of subacute bacterial endocarditis. In 66 per cent of these "high altitude" rats bacterial endocarditis developed as compared with a control group of 15 per cent. Lillehei and his co-workers[1] noted that bacterial endocarditis developed "spontaneously" in 70 per cent of animals with iliofemoral arteriovenous fistulas. They then initiated a study in which the creation of bilateral fistulas and injection of beta hemolytic streptococci produced bacteremia in 100 per cent of dogs.[2] They concluded that the original stress was more important than infection in producing the disease and postulated an increased endothelial susceptibility as one result of that stress. Gowdy and his associates[13] were able to produce endocardial lesions within 6 to 12 hours after huge (2 to 4.5 cm.) aortocaval shunts had been created in dogs. These large fistulas were noted to prolong definitely the time required to remove the bacteria from the blood stream.

Holman[14] has fully considered the important cardiovascular changes that occur when a large arteriovenous fistula is opened. The pathogenic relationships involved in the production of the endocarditis in dogs can be summarized as follows: the fistula causes an overloading of the venous system by allowing the shunting of large volumes of arterial blood. An increase in the circulating blood volume, the cardiac rate and the cardiac work then occurs. The shunt also causes a local vena caval lesion to form which becomes infected by the repeated intravenous administration of organisms. The blood stream is thus continuously supplied with bacteria. The exact mechanism whereby the increased cardiovascular stress sets up the valvular endothelial localization is not known, but it would appear that increased hemic trauma to the valve is, at least partly, responsible. The observations of the spontaneous closure (functional or anatomic or both) and of the healed caval lesions of the fistulas in the seven dogs without endocarditis, in spite of the administration of great numbers of bacteria, makes the following conclusions possible: One, that a maintained stress in the form of a widely patent fistula is one of the chief factors necessary to infect the valves. Two, that the first lesion to form is probably a sterile "jet" lesion whose subsequent fate depends on the continued stress and on bacteremia. Our experience confirms that of Holman[14] and of Lillehei and co-workers[1, 2] that the size of the anastomosis is an important consideration in experiments of this type. There is a tendency for shunts smaller than the "critical" size (probably 10 mm. in aortocaval fistulas in dogs) to undergo fibrotic closure, while shunts larger than this tend to increase in size from the increased blood volume and enlargement of the proximal segment of the artery with more blood being shunted. Thus, a vicious cycle is instituted.

The most important factor in the failure to produce bacterial endocarditis in some of these dogs is the spontaneous closure of the fistula. Another factor may have been the type of organism, since it is known that *Streptococcus*

mitis is a relatively avirulent organism in comparison with the hemolytic streptococci used in the majority of other studies. Increased dosage of bacteria beyond a certain point did not seem to be a factor in the production of endocarditis. This conclusion is in agreement with the experience of the Lillehei group.[2] Five dogs died from causes other than endocarditis. All had early and persistent blood stream infections. They lived as long as did the dogs with endocarditis and all had widely patent fistulas at necropsy. It is difficult to explain why endocarditis did not develop in these animals.

Evaluation of therapeutic regimens of this type of experimental endocarditis, in which a weakly virulent organism is used, would require a method in which endocarditis developed in a larger number of animals. Further work in this direction is justified before attempting studies on the effects of antibacterial therapy and the surgical closure of the anastomoses.

Summary

Streptococcus mitis endocarditis was produced in 50 per cent of 24 dogs by the intravenous administration of this organism following the creation of aorto-vena caval shunts. Infection was accomplished by daily injections of 10 ml. of a 24-hour broth culture of *Streptococcus mitis* for at least 14 consecutive days. Persistent bacteremia became manifest within 11 days. In two animals (one with endocarditis) additional injections of 20 cc. of the culture three times per day were required to establish bacteremia. Failure to produce bacterial endocarditis in 50 per cent of the animals was associated with contracted or closed fistulas in seven of these twelve animals. In the remaining five animals, death occurred from other causes. It thus appeared that the presence of an adequately patent fistula is necessary for the development of endocarditis. Eleven animals died from their endocarditis. Five others died from pulmonary and embolic septicemia. *Streptococcus mitis* was consistently recovered from the valvular and vena caval vegetations. The pathogenesis of this experimentally induced bacterial endocarditis is discussed briefly.

Summario in Interlingua

In 12 casos ex un gruppo de 24 canes, endocarditis a *Streptococcus mitis* resultava del administration intravenose de ille organismo post le creation de derivationes inter aorta e vena cave. Le infection esseva complite per le injection diurne, durante un continue periodo de al minus 14 dies, de 10 ml de un cultura a bouillon de *S. mitis* de un maturitate de 24 horas. Bacteremia persistente se manifestava intra 11 dies. In duo animales—un con endocarditis—bacteremia resultava solo de injectiones additional de 20 cc del bouillon tres vices per die. Inter le 12 animales que non disveloppava endocarditis bacterial il habeva septe casos in que iste facto esseva associate con le presentia de fistulas contrahite o claudite. In le remanente cinque casos de iste gruppo altere causas resultava in le morte del animal. Per consequente il pare que le disveloppamento de endocarditis require le presentia de un fistula a apertura adequate. Dece-un del animales moriva de lor endocarditis. Cinque alteres moriva de septicemia pulmonar e embolic. In omne casos *S. mitis* esseva constatate in le vegetation del valvulas e del vena cave. Es presentate un breve discussion del pathogenese de iste typo experimental de endocarditis bacterial.

REFERENCES

[1] Lillehei, C. W., Bobb, J. R. R., and Visscher, M. B.: The occurrence of endocarditis with valvular deformities in dogs with arteriovenous fistulas. Ann. Surg. **132:** 577, 1950.

[2] —, Shaffer, J. M., Spink, W. W., Bobb, J. R. R., Wargo, J. D., and Visscher, M. B.: Role of cardiovascular stress in the pathogenesis of endocarditis and glomerulonephritis: Observations including method of experimental production utilizing arteriovenous fistulas. A. M. A. Arch. Surg. **63:** 421, 1951.

[3] Abbott, M. E.: Atlas of Congenital Cardiac Disease. New York, American Heart Association, 1936.

[4] Rienhoff, W. F., Jr., and Hamman, Louis: Subacute streptococcus viridans septicemia cured by excision of an arteriovenous aneurysm of the external iliac artery and vein. Ann. Surg. **102:** 905, 1935.

[5] Williams, M. H.: Traumatic arteriovenous aneurysm associated with streptococcic septicemia: Report of a case with cure following

penicillin therapy and operation. J.A.M.A. **148:** 726, 1952.

[6] CUTLER, S. S., AND WOLF, JULIUS: Acquired arteriovenous fistula with coexistent subacute bacterial endocarditis and endarteritis. Ann. Int. Med. **25:** 972, 1946.

[7] ALLEN, A. C.: Mechanism of localization of vegetations of bacterial endocarditis. Arch. Path. **27:** 399, 1939.

[8] ALLEN, A. C.: A case of bacterial endocarditis illustrating the mechanism of localization and the nature of vegetations. Am. Heart J. **21:** 667, 1941.

[9] NEDZEL, A. J.: Experimental endocarditis. Arch. Path. **24:** 143, 1937.

[10] VISSCHER, M. B., AND HENSCHEL, AUSTIN: The relation of age and other factors to cardiac subendothelial hemorrhage in dogs. Am. Heart J. **30:** 592, 1945.

[11] HIGHMAN, BENJAMIN, AND ALTLAND, P. D.: Acclimatization response and pathologic changes in rats at an altitude of 25,000 feet. Arch. Path. **48:** 503, 1949.

[12] HIGHMAN, BENJAMIN, AND ALTLAND, P. D.: A new method for the production of experimental bacterial endocarditis. Proc. Soc. Exper. Biol. & Med. **75:** 573, 1950.

[13] GOWDY, R. A., MARTIN, S. P., KERBY, G. P., AND SEALY, W. C.: Pathogenesis of valvular endocarditis: I. Production of acute cardiac vascular lesions by a large arteriovenous shunt. II. Effects of an arteriovenous shunt on removal of bacteria from the blood stream. A.M.A. Arch. Surg. **65:** 271, 1952.

[14] HOLMAN, EMILE: Arteriovenous Aneurysm: Abnormal Communications Between the Arterial and Venous Circulations. New York, The Macmillan Company, 1937.

Experimental Bacterial Endocarditis Due to Streptococcus Mitis

II. Pathology of Valvular and Secondary Lesions

By Robert A. Rabens, M.D., Alfred G. Karlson, Ph.D., Joseph E. Geraci, M.D., and Jesse E. Edwards, M.D.

Pathologic and bacteriologic studies were carried out in all 24 dogs subjected to arteriovenous anastomoses and bacteremia. The single etiologic agent, *Streptococcus mitis*, was stained and cultured from 10 of the 11 hearts with active endocarditis (one animal had a healed tricuspid valvulitis) and from 16 of 17 animals with patent fistulas and active caval vegetations. The latter lesions occurred shortly after the initiation of injections and served as an important source of bacteria to the blood stream and heart valves. The endocarditis resembled that found in human cases with destructive and reparative phenomena coexisting. Focal myocarditic lesions and cardiac failure were noted only in animals with endocarditis. The other secondary (embolic) lesions were similar to those seen in man with the exception that in the dog the lesions had a suppurative tendency. Acute diffuse proliferative glomerulonephritis was found in animals with endocarditis and in those with infected fistulas and bacteremia.

IN A companion communication the method of inducing experimental bacterial endocarditis in dogs with *Streptococcus mitis* is described. Following the pioneer work of Lillehei and associates[1-3] the method entailed creation either of aorto-inferior vena caval fistulas or of bilateral iliofemoral arteriovenous fistulas followed by intravenous administration of *Streptococcus mitis*.* Among 24 dogs so treated, pathologic evidence of bacterial endocarditis was obtained in 12. Eleven of these animals (group IA) died of their induced disease from 7 to 128 days after the clinical signs of bacterial endocarditis, and each had evidence of the disease at necropsy. Another animal (group IB) had pathologic evidence suggesting that active endocarditis had been present but had healed spontaneously. This animal had not shown clinical signs of bacterial endocarditis and was killed by intravenous administration of a barbiturate 202 days after the administration of the bacteria was begun.

This paper will describe the pathologic findings in 12 animals with endocarditis and will compare them with the findings in the remaining 12 animals without endocarditis. Of the 12 animals which had no pathologic evidence of endocarditis, five died of septicemia and pulmonary infarction resulting from the infected fistulas (group IIA). The other seven animals remained healthy and when killed were found to have complete or nearly complete closure of their fistulas (group IIB). These had no evidence of valvular involvement or infection of the fistulas nor were any significant lesions found in the other organs; these seven animals will not be considered further in this report.

Pathologic Findings

Eleven Animals With Active Bacterial Endocarditis (Group IA): Five Animals With No Endocarditis but With Infected Arteriovenous Fistulas (Group IIA)

In each of the animals with active bacterial endocarditis there had been consistently positive blood cultures with *S. mitis*. Cultures of representative valvular vegetations, performed in 10 of the animals, revealed *S. mitis*. Also in each animal, except one, *S. mitis* was demonstrated at the site of the arteriovenous fistula in vegetations on the edges of the anastomoses and on the luminal surface of the

Abridgment of portion of thesis submitted by Dr. Rabens to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Medicine. The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

* We are indebted to Drs. J. M. Janes and R. Thors for performing the surgical procedures in the majority of the animals.

TABLE 1.—*Locations of Bacterial Endocarditis in 11 Animals With Active Bacterial Endocarditis (Group IA)*

Animal	Valves Affected		
	Aortic	Mitral	Other
1	+		
2	+		
3	+	+	Tricuspid
4	+	+	Pulmonary
5	+		
6	+	+	
7	+		
8		+	
9	+		
10		+	Tricuspid
11	+	+	Tricuspid
Total	9	6	4

vein opposite the fistula. In each of the animals of group IIA, the blood cultures remained consistently positive and the arteriovenous hunts were also infected.

Cardiac Valves.—In the table is summarized the location of the valvular vegetations in the 11 animals with active endocarditis. In each animal there was involvement of one of the left-sided valves. In four animals both mitral and aortic valves were involved; in two of the latter there was also involvement of the tricuspid valve and in a third there was involvement of the pulmonary valve. In a case wherein the mitral valve was the only site of a lesion on the left side, there was also involvement of the tricuspid valve.

The gross appearance of the vegetations was typical of those seen in bacterial endocarditis (fig. 1). The vegetations were soft, friable, polypoid and gray to purple. They varied considerably in size from superficial deposits to fungating masses. Evidence for destruction of the valve leaflets related to the deposition of vegetations was common. The valvular tissue frequently showed fibrous thickening associated with vascularity of the base of the

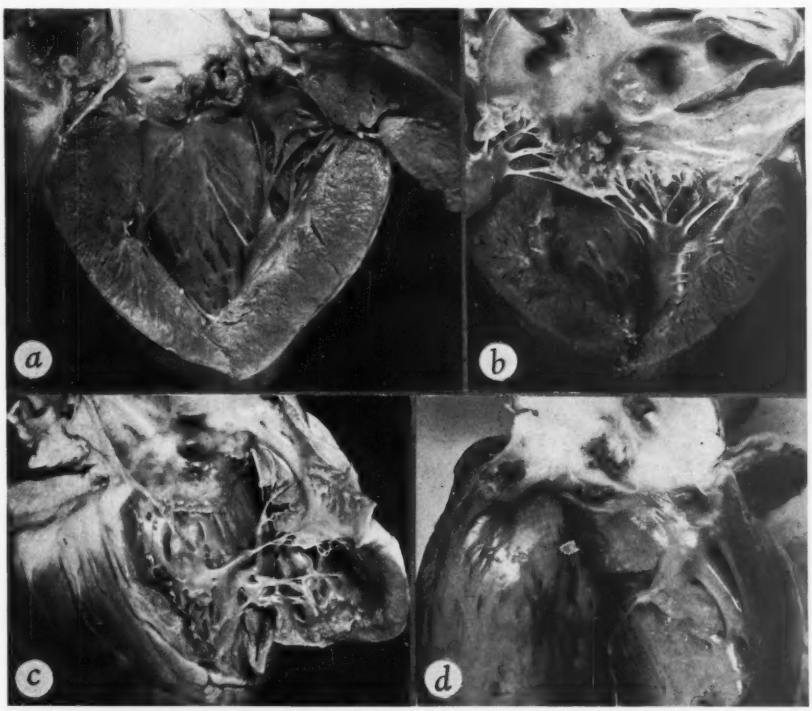


FIG. 1. Gross specimens of hearts with bacterial endocarditis. *a*. Left ventricle. Involvement of aortic valve. *b*. Left atrium and ventricle. Involvement of mitral valve. *c*. Right atrium and ventricle. Tricuspid valve involved in an animal whose heart is illustrated in *b*. *d*. Pulmonary valve involvement and secondary infective lesion in pulmonary trunk.

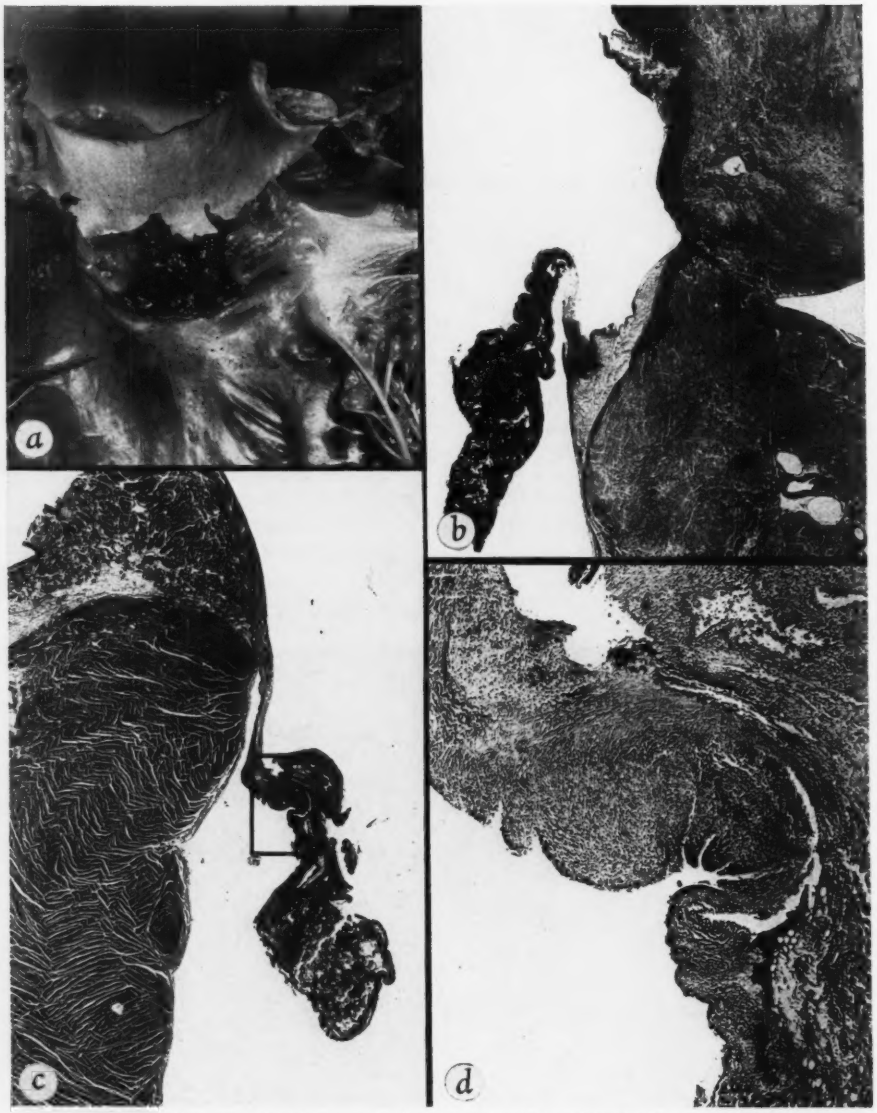


FIG. 2*a*. The aortic valve showing vegetations of bacterial endocarditis associated with destruction of adjacent portions of right and posterior leaflets. *b*. Aortic valve and adjacent structures showing vegetations of bacterial endocarditis involving aortic valve. In the ascending aorta there is a focus of infection associated with destruction of the aortic wall and cellular infiltration in tissues about the aorta. (Elastic tissue stain ×7.) *c*. Posterior leaflet of mitral valve and adjacent structures showing vegetations of bacterial endocarditis involving valve leaflet. Area within rectangle illustrated in greater detail in *d*. (Hematoxylin and eosin;×7.) *d*. Higher power of segment of mitral valve illustrated in *c* showing bacterial colonies in vegetation, destruction of valvular tissue and granulation tissue in relation to vegetation. (Hematoxylin and eosin; ×50.)

valve leaflet. The commonest site of deposition of vegetations was on the contact face of the leaflets. Secondary mural endocarditis was common. In several instances wherein the aortic valve was involved, there was associated infection of the ascending aorta accompanied by the formation of mycotic aneurysm (fig. 2*a* and *b*).

Microscopically, the active bacterial endocarditis was represented by necrosis of valvular tissue associated with deposition of the vegetations containing colonies of gram-positive cocci (fig. 2*c* and *d*). Adjacent to the site of deposition of vegetations there was granulation tissue containing varying numbers of leukocytes including neutrophilic granulocytes and monocytes. Abscess formation of the valve leaflets was occasionally seen. No pericarditis was present in any of the animals.

Myocardium.—Microscopically, it was possible to divide the myocardial lesions into focal and diffuse types. Focal myocardial lesions were further divided into the following forms: (*a*) focal myocarditis, (*b*) abscesses, (*c*) microinfarcts and (*d*) lesions of the myocardial vessels. The focal lesions were seen only in animals of group IA with the exception that such a lesion was seen in an animal of group IIA. Diffuse myocardial lesions were seen in members of both groups IA and IIA but primarily in the former.

Focal myocarditis consisted of small areas

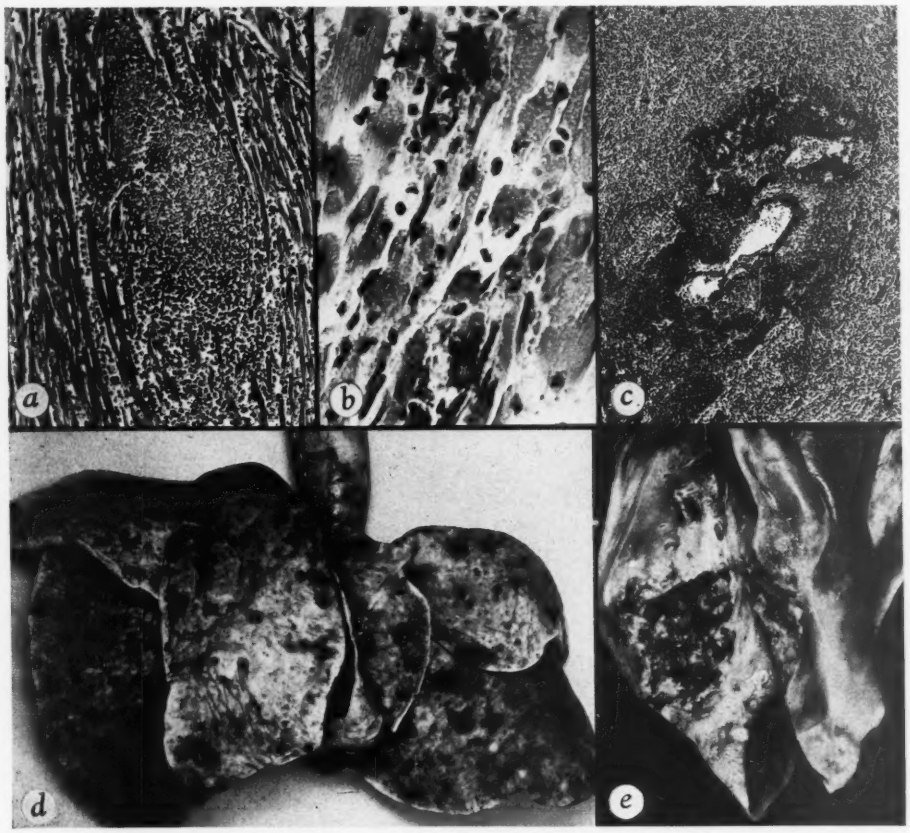


FIG. 3. Photomicrographs of heart. *a*. Myocardium of animal with bacterial endocarditis showing a small infarct and early abscess formation. (Hematoxylin and eosin;×100.) *b*. Two microinfarcts in myocardium of an animal with active bacterial endocarditis. (Hematoxylin and eosin;×425.) *c*. The posterior descending coronary artery in an animal that had an infected arteriovenous fistula but no endocarditis. Destructive suppurative arteritis associated with suppuration in surrounding epicardium and myocardium. (Hematoxylin and eosin;×50.) *d*. Gross view of lungs in an animal of group IIA having an infected arteriovenous fistula but no bacterial endocarditis. Multiple hemorrhagic and infected infarcts. *e*. In an animal of group IIA abscess formation complicating an infected infarct. Hemorrhage into the adjacent pleural space had occurred from this lesion, leading to the death of the animal.

of increased cellularity (polymorphonuclears, mononuclears, myocytes and young fibroblasts) usually situated perivascularly. There was no evidence of necrosis. No Aschoff nodules were seen. This lesion was observed in all animals of group IA (active endocarditis).

Microabscesses appeared as focal areas of necrosis which were well circumscribed, containing many polymorphonuclears of all ages, bacterial clumps and cellular debris with a peripheral zone of dense cellularity but without capsule formation (fig. 3*a*). These lesions were found singly and in groups, probably representing what were originally septic infarcts. Abscesses of the myocardium were observed exclusively in 6 cases with active endocarditis (group IA).

Microinfarcts consisted of multiple, tiny focal areas of necrosis of muscle in which there were no nuclei, and increased eosinophilic staining of the muscle fibers (fig. 3*b*). While some removal of muscle fibers occurred, completely healed infarcts were not seen. Gross myocardial infarcts were noted in only two animals with endocarditis. One animal of group IIA (fig. 3*c*) had an embolic occlusion of the posterior descending coronary artery associated with suppurative arteritis and surrounding epicarditis and myocarditis.

Lesions of the myocardial vessels included multiple bacterial emboli within the small arteries and arterioles in five animals of group IA. These consisted of unorganized vegetations containing cells which chiefly were polymorphonuclear leukocytes and colonies of streptococci. In one of these animals, acute angiitis with marked cellular infiltration of the vessel wall was also present.

Diffuse myocarditis was characterized by widespread interstitial collections of polymorphonuclears, mononuclears, an occasional Anitschkow myocyte and young and mature fibroblasts. The myocardial fibers themselves were undamaged. This lesion was noted in all but two of the animals with endocarditis (group IA) and was evident in two of the five animals of group IIA.

Lungs.—Each of the 11 animals in group IA had lungs much heavier than normal on the basis of extensive edema. In seven of these there were additionally many foci of hemorrhage. On microscopic examination the latter were seen to represent areas of infarction. In the areas of infarction the alveoli contained infiltrating cells which for the most part were neutrophilic leukocytes. Abscess formation surrounded by granulation tissue of varying ages also occurred in such areas. An occasional artery related to areas of infarction contained embolic material heavily laden with bacterial colonies.

Similarly infarcted areas were present in each of the five animals of group IIA (fig. 3*d*). In the latter group the lungs were not edematous to an appreciable degree. One animal in the latter group had extensive pleural hemorrhage originating in a pulmonary infarct that had progressed to abscess formation (fig. 3*e*).

Kidneys.—In five of the animals in group IA the kidneys were somewhat enlarged and showed many petechial hemorrhages involving the cortices. In four of these animals the microscopic appearance of the kidneys showed an increased cellularity of most of the glomerular tufts associated with mild thickening of the basement membranes (fig. 4*a*). Glomerular and tubular hemorrhages were also present. One of these four animals also showed bacterial emboli in renal arterioles and capillaries, and in this animal there was focal necrosis of glomerular tufts. In the fifth animal of group IA with gross petechial hemorrhages, there was not present the diffuse glomerulitis just described. This animal had glomerular and tubular hemorrhages, focal necrosis of glomerular tufts with hyalinized thrombi and bacterial emboli in small vessels (fig. 4*b*).

In a sixth animal of group IA, the only renal lesions were represented by massive infarction of the lower pole of each organ. In the infarcted area there were multiple small abscesses containing bacterial colonies on microscopic examination.

In the remaining five animals of group IA, no acute renal lesions were present.

The only acute type of renal disease seen in animals of group IIA was the diffuse glomerulitis already described for animals of group IA. This occurred in one animal.

It is of passing interest that in 22 of the 24

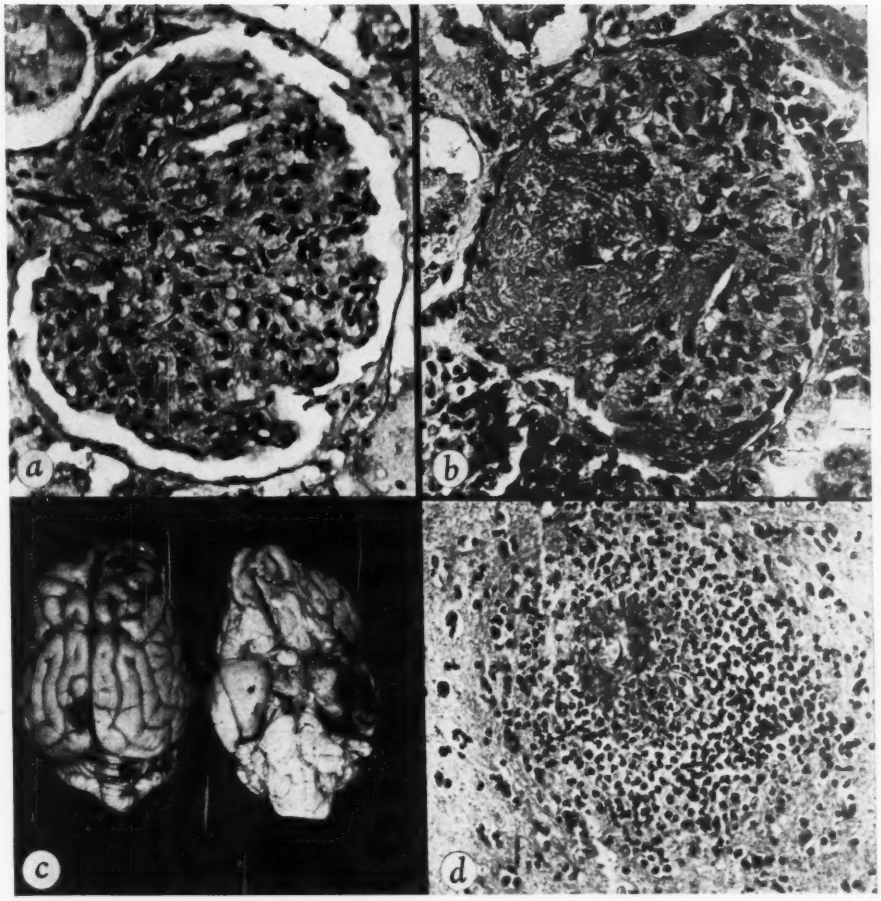


FIG. 4*a*. Renal glomerulus in an animal with bacterial endocarditis and diffuse acute glomerulonephritis. Cellular proliferation of tuft. (Hematoxylin and eosin; ×320.) *b*. Renal glomerulus in an animal with bacterial endocarditis and focal glomerulitis. Focal necrosis of glomerular tuft. Cellular proliferation. (Hematoxylin and eosin; ×300.) *c*. Superior and inferior surfaces of brain in an animal with bacterial endocarditis. Multiple hemorrhagic infarcts. *d*. Photomicrograph of brain in an animal with bacterial endocarditis. Microabscess. (Hematoxylin and eosin; ×250.)

animals which were the subjects of these experiments, a chronic, low-grade interstitial nephritis was present. In some this was associated with gross scars in the cortex. These lesions are considered to represent spontaneous disease of the animal and not to be related to the experiments performed.

Brain.—Gross hemorrhages or petechial hemorrhages were visible in all components of the brain in 7 of the 11 animals in group IA (fig. 4*c*). On histologic examination, microscopic infarcts were seen in each of the animals in group IA. The infarcts consisted of areas of perivascular necrosis associated with a proliferation of oligodendroglia and astrocytes. Microabscesses of the brain were seen in four animals with endocarditis (fig. 4*d*); the adjacent small vessels frequently contained clumps of cocci. In two animals with active endocarditis an acute purulent leptomeningitis was present.

Among the five animals of group IIA, one had disseminated infarcts of the brain and also had a mycotic aneurysm of an artery in the

meninges. The aneurysm ruptured, leading to subarachnoid and intracerebral hemorrhages. This is the same animal in which suppurative arteritis of a coronary artery has been described.

Spleen.—In six of the animals of group IA and in each animal of group IIA the spleen was enlarged. In seven of the animals of group IA, infarcts of varying ages, some of which were healed, were present. None in group IIA had splenic infarcts.

Liver.—No embolic lesions were evident in the liver. In the majority of animals of group IA, there was evidence of chronic passive congestion. In some of these, central hemorrhagic necrosis was also present. It was considered that the hepatic changes were manifestations of congestive cardiac failure.

Adrenals.—No histopathologic evidence of adrenal cortical hypertrophy was found in any of the animals.

One Animal With Healed Bacterial Endocarditis (Group IB)

One animal presented a thickened septal leaflet of the tricuspid valve. Histologically, the valve showed an acellular swollen appearance with capillary ingrowth and marked fragmentation of the collagenous structure. The changes were interpreted as representing healed bacterial endocarditis. No lesions were observed in either the mitral valve or the aortic valve. The myocardium was of normal appearance.

The inferior vena cava opposite the patent anastomotic site was thickened and scarred, with a few granular elevations. The only other lesions were several healed infarcts of the lung and an old fibrous perisplenitis.

Comment

In comparison with human cases of endocarditis due to *Streptococcus mitis*, the secondary lesions in the dog were more active and suppurative in nature. It is interesting to consider which of the secondary lesions in the body were due to the presence of the bacterial endocarditis and which may have been related to the existence of infection of the arteriovenous fistula. A convenient manner of considering this problem comes from the comparison of the 11 animals with active bacterial endocarditis and infected fistulas on one hand, and the five animals without bacterial endocarditis but with infected fistulas on the other.

Lesions of the myocardium of a focal nature were, with one exception, found only in the cases with bacterial endocarditis, leading to the interpretation that they were the result of emboli from the cardiac valves. The myocardial lesions of focal nature were essentially like those described in man with subacute bacterial endocarditis.[4-7] Diffuse interstitial myocarditis was present not only in the animals having bacterial endocarditis, but also in the animals with infected arteriovenous fistulas but without endocarditis. It is impossible to prove whether this represents a hypersensitivity response to the presence of infection with *S. mitis* or the result of bacteria reaching the myocardium.

In the lungs the disseminated infarcts, many of which were obviously infected, may be related to the existence of the infected fistula. In the cases wherein endocarditis involved the tricuspid or pulmonary valve, the pulmonary infarcts may have been due to emboli either from the fistula or from the infected valve.

The pulmonary edema, which was prominent only in the animals with bacterial endocarditis, is considered an expression of cardiac failure. The mechanism or mechanisms by which cardiac failure occurred leading to pulmonary edema are probably the same as apply to human cases of bacterial endocarditis with cardiac failure. Destructive lesions of the cardiac valves alone, the presence of secondary myocardial lesions alone, or the two combined could have contributed to the failure of the heart.

The lesions of the kidneys which were acute, which seemed related to the experimental procedures and which resembled lesions previously described in experimental endocarditis were of two types. One was characterized by a diffuse glomerulonephritis simulating the acute type that Lillehei and associates[2] found and that Bell[8] described as occurring as a subclinical entity in 50 per cent of clinical cases of

subacute bacterial endocarditis. The second type of lesion presented the picture of a focal glomerulitis associated with demonstrable bacteria in the small blood vessels. This occurred in two animals of the series, both with endocarditis. This lesion resembled one of the two types described by Bell;[8] that is, exhibiting hyalinized intracapillary thrombi with capillary necrosis. Each of the two animals with the latter type of lesion had bacterial endocarditis, while among the animals having the former (diffuse) type of renal disease, there were four cases of bacterial endocarditis and one of infected arteriovenous fistula without endocarditis.

The lesions in the brain were commonly present in the animals with bacterial endocarditis. They occurred in only one animal without endocarditis but with an infected arteriovenous fistula. The cerebral lesions characterized by infarction and abscess formation were frequently associated with bacterial emboli, thus indicating that they were caused by particles of the valvular vegetation which had broken off and had been carried by the blood stream to the brain. The one case which remains an enigma is that of the animal in the group without endocarditis, but in which the cerebral lesions were the same as in the animals with endocarditis. Moreover, this animal had a mycotic aneurysm of a cerebral artery leading to rupture and cerebral hemorrhage. In the same animal, it will be recalled, there was a focus of acute suppurative arteritis in the posterior descending coronary artery. From the secondary lesions one would consider strongly that bacterial endocarditis had been present in this animal, but re-study of the specimen of heart failed to reveal any evidence that bacterial endocarditis had existed. One might attribute the lesions of this animal simply to septicemia, but it seems more reasonable to conclude that particles of infected blood clots had been lodged in vessels of the brain and the heart. With the cardiac valves eliminated as a source for such emboli, it is possible that in relation to one or more pulmonary infarcts, infected thrombi were present in pulmonary veins leading to systemic emboli. No such lesions were found, but since no detailed study of the pulmonary veins had been made, this remains as a possibility which cannot be either proved or disproved.

Summary

The pathologic features are described of experimentally induced endocarditis with *Streptococcus mitis* in dogs having surgically created systemic arteriovenous fistulas.

The changes resemble those seen in human cases of subacute bacterial endocarditis with the exception that in the dog the secondary lesions had a tendency to be suppurative.

Comparison of the pathologic findings in the animals having bacterial endocarditis and infected arteriovenous fistulas on one hand with the findings in animals having only infected arteriovenous fistulas on the other hand revealed certain similarities and certain differences. Myocarditis of focal nature was seen, with one exception, only in animals with bacterial endocarditis, while diffuse myocarditis was observed in both groups. Cardiac failure was evident only in the animals with endocarditis. Examples of glomerulonephritis were seen in animals with bacterial endocarditis and in those having only infected arteriovenous fistulas.

Summario in Interlingua

Es describite le characteristicas pathologic de endocarditis producite experimentalmente in canes per le injection de *Streptococcus mitis* post le creation chirurgic de fistulas arteriovenose in le circulation systemic.

Le alterationes observate es simile a illos in patientes human con subacute endocarditis bacterial, excepte que in le canes le lesiones secundari manifestava un tendentia suppurative.

Esseva comparate ab le puncto de vista del constatationes pathologic le casos de animales que habeva endocarditis bacterial e inficite fistulas arteriovenose con le casos de animales que habeva solo inficite fistulas arteriovenose. Iste comparation revelava certe similaritates e certe differentias. Myocarditis de character focal esseva observate—con un sol exception—exclusivemente in animales con endocarditis bacterial, sed myocarditis diffuse esseva ob-

servate in ambe gruppos. Insufficientia cardiac se manifestava solo in animales con endocarditis. Exemplos de globerulonephritis esseva vidite tanto in animales con endocarditis bacterial como etiam in animales que habeva solo inficite fistulas arteriovenose.

REFERENCES

[1] Lillehei, C. W., Bobb, J. R. R. and Visscher, M. B.: The occurrence of endocarditis with valvular deformities in dogs with arteriovenous fistulas. Ann. Surg **132:** 577, 1950.

[2] —, Bobb, J. R. R., Wargo, D., Visscher, M. B., Shaffer, J. M. and Bell, E. T.: Experimental production of diffuse proliferative glomerulonephritis utilizing arteriovenous fistula stress with bacteremia. Circulation. **4:** 587, 1951.

[3] —, Shaffer, J. M., Spink, W. W., Bobb, J. R. R., Wargo, J. D. and Visscher, M. B.: Role of cardiovascular stress in the pathogenesis of endocarditis and glomerulonephritis. A.M.A. Arch. Surg. **63:** 421, 1951.

[4] Saphir, O.: Myocardial lesions in subacute bacterial endocarditis. Am. J. Path. **11:** 143, 1935.

[5] Saphir, O., Katz, L. N. and Gore, I.: Myocardium in subacute bacterial endocarditis. Circulation. **1:** 1155, 1950.

[6] De Navasquez, S.: The incidence and pathogenesis of myocardial lesions in subacute bacterial endocarditis. J. Path. & Bact. **49:** 33, 1939.

[7] Perry, E. L., Fleming, R. G. and Edwards, J. E.: Myocardial lesions in subacute bacterial endocarditis. Ann. Int. Med. **36:** 126, 1952.

[8] Bell, E. T.: Renal Diseases. Ed. 2. Philadelphia, Lea & Febiger, 1950.

Right Ventricular Hypertrophy

I. Correlation of Isolated Right Ventricular Hypertrophy at Autopsy with the Electrocardiographic Findings

By Isom C. Walker, Jr., M.D., Robert A. Helm, M.D., and Ralph C. Scott, M.D.

The electrocardiograms of 22 cases showing isolated right ventricular hypertrophy at autopsy were examined for changes suggestive of right ventricular hypertrophy. Only 5 of 22 cases fulfilled at least one of the criteria of Sokolow and Lyon and only three could be diagnosed as having right ventricular hypertrophy by the criteria of Myers, Klein and Stofer. Factors contributing to the development of electrocardiographic changes of right ventricular hypertrophy are discussed.

THE DIAGNOSIS of enlargment of the right ventricle is difficult notwithstanding the use of all available methods of study. The teleoroentgenogram of the chest is relatively unreliable. In a study of 39 cases of cor pulmonale proved by autopsy, Zimmerman and Ryan[1] found x-ray evidence of a large pulmonary artery segment or right ventricular enlargement in only six instances. Spain and Handler[2] stated only "a few" of the 60 cases of cor pulmonale which they examined at autopsy had shown radiologic evidence of right ventricular hypertrophy. Sussman, Grishman and Steinberg[3] studied 28 cases of emphysema radiographically and found no heart greater than the predicted size on the posterioanterior view. By angiocardiograms 12 of these cases presented right ventricular dilatation and an additional 12 cases showed questionable dilatation.

Several papers have been published concerning the reliability of the electrocardiogram in the diagnosis of right ventricular hypertrophy.[4-9] Berlinger and Master[7] using the standard limb leads correlated the autopsy and electrocardiographic findings in mitral stenosis. The electrocardiogram demonstrated right ventricular preponderance in 40 of 45 cases and a "trend" to right ventricular preponderance in 11 of 12 cases. Katz and his co-workers[8] found positive electrocardiographic findings in seven of eight cases of anatomically demonstrated right ventricular preponderance. In autopsy studies of cor pulmonale Spain and Handler,[2] and Zimmerman and Ryan[1] reported the presence of right axis deviation in 14 of 21, and 23 of 43 cases, respectively.

More recently several studies have been reported using the unipolar limb and precordial leads. Levine and Phillips[5] found electrocardiographic evidence of right ventricular hypertrophy in 8 of 10 autopsy-proven cases of right ventricular hypertrophy. Myers, Klein and Stofer[4] reported 40 autopsied cases of anatomic right ventricular preponderance. Thirty-three of these showed either the electrocardiographic pattern of right ventricular hypertrophy or right bundle-branch block. Sokolow and Lyon[6] set up criteria for the electrocardiographic diagnosis of right ventricular hypertrophy from 60 cases. Only six of these were proven by autopsy. The diagnosis was established at surgery in 20 and by angiocardiograms in seven. Forty-five of the 60 cases had congenital heart disease and 40 per cent were five years of age or younger.

All previous reports were based on right ventricular preponderance rather than isolated right ventricular hypertrophy. In general, cardiac muscle mass is considered to determine the direction of the mean electrical vector and the resultant electrocardiographic pattern. Coexisting left and right ventricular hypertrophy tend to obscure the electrocardiographic

From the Cardiac Laboratory, Cincinnati General Hospital and the Department of Internal Medicine, College of Medicine, University of Cincinnati, Cincinnati, Ohio.

Dr. Helm is a Public Health Service Research Fellow of the National Heart Institute.

pattern of the other.[10] Therefore, isolated hypertrophy of the right ventricle should give a high anatomic-electrocardiographic correlation. Since the authors could find no report in which an attempt has been made to correlate isolated right ventricular hypertrophy proven at autopsy and the electrocardiographic patterns encountered, the present study was undertaken.

Method

The autopsy records of cases over 12 years of age at the Cincinnati General Hospital were examined for cases showing isolated right ventricular hypertrophy. This diagnosis was made pathologically according to the following criteria: (1) a heart weight exceeding the mean standard deviation from normal for body weight[11]; (2) a right ventricular thickness of 5 mm. or greater[1, 2, 12, 13] or of 4 mm. when a specific statement was made that the right ventricle was dilated; (3) a left ventricular thickness of 13 mm. or less. That isolated right ventricular hypertrophy, on the basis of these criteria, is relatively uncommon is indicated by the fact that only 82 cases were found during the years 1948 through 1953. Approximately 4,000 autopsies were performed in this six-year period. Only 22 cases fulfilling the above criteria had, within two months before death, a 12-lead electrocardiogram which showed no evidence of either myocardial infarction or complete bundle-branch block. One case of incomplete right bundle-branch block was included in the study. The electrocardiograms on these 22 cases were examined and compared with the criteria of Myers, Klein and Stofer,[4]* and of Sokolow and Lyon.[6]†

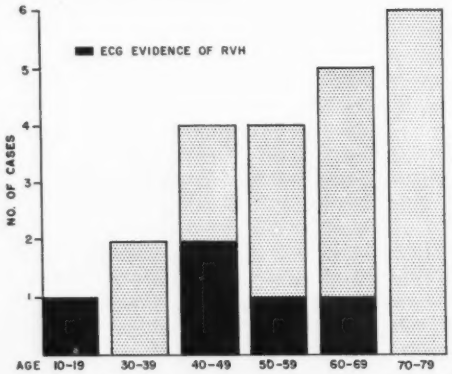


FIG. 1. Result of anatomic–electrocardiographic correlation presented according to age groups.

Results

No predominant age group or heart weight for patients whose electrocardiograms showed evidence of right ventricular hypertrophy is demonstrated in figures 1 and 2. Figure 3 suggests that electrocardiographic evidence of right ventricular hypertrophy may occur more frequently, the thicker the right ventricle. Figure 5, however, shows no relationship between the right ventricle-left ventricle thickness and the presence of electrocardiographic evidence of right ventricular hypertrophy. Table 1 shows the analysis of the electrocardiograms on the 22 cases studied and table 2 compares these findings with (1) criteria proposed by Sokolow and Lyon,[6] (2) criteria of Myers, Klein and Stofer,[4] (3) abnormal "P" waves,[14] (4) right ventricular hypertrophy as suggested by the standard limb leads.[7]

* The criteria for the diagnosis of right ventricular hypertrophy presented by Myers, Klein and Stofer are in general terms rather than specific numbers. They divided their cases into groups outlined below. An electrocardiogram fulfilling the criteria of any of the major groups, that is A, B, C, D, or E, was considered to demonstrate electrocardiographic evidence of right ventricular hypertrophy.

A. Pattern of right ventricular hypertrophy in leads V_1 to V_6. (1) Reversal in ratio of the amplitudes of the R and S waves in V_1 and V_6 characterized by an abnormally large R in proportion to S in V_1, a diminution in ratio in leads further to the left, and a prominent S in V_6. (2) Time interval from beginning of QRS to onset of intrinsicoid deflection that was abnormally long in V_1 (generally between 0.03 and 0.05 second) and greater than in V_5 or V_6. (3) Tendency to a small Q wave in V_1. (4) Tendency to inversion of the T wave in V_1, and to upright T wave in V_6. (5) Total duration of QRS less than 0.12 second and generally within the normal range. (6) Absence of notching or double peaking of the R wave in V_1.

B. Pattern of right ventricular hypertrophy or incomplete right bundle-branch block in lead V_{3R}, and not in V_1 or V_2.

C. Pattern presumptive of right ventricular hypertrophy in V_6 and aV_R without confirmatory signs in V_1 or V_2.

D. Incomplete right bundle-branch block. (1) In leads from right side of precordium, R wave prominent and exhibited either a coarse notch or double peak and S wave small or absent, whereas, in leads further to the left, S wave deeper and broader. (2) Time interval from beginning of QRS to onset of intrinsicoid deflection in V_1 between 0.05 and 0.07 second. (3) Total duration of QRS less than 0.1 second. (4) Absence of Q wave in leads from right precordium.

E. Complete right bundle-branch block.

† The specific criteria for right ventricular hypertrophy of Sokolow and Lyon are given in table 2.

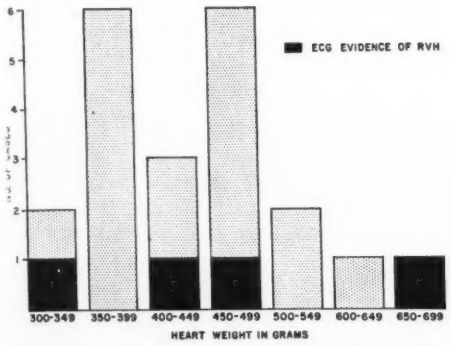


FIG. 2. Result of anatomic–electrocardiographic correlation presented according to heart weight. (Note: one heart not weighed.)

Five of the 22 cases fulfilled at least one of Sokolow and Lyon's criteria for right ventricular hypertrophy. No single criterion was outstanding. An S wave in V_5 or V_6 of 7 mm. or greater, R of V_1 + S of V_5 or V_6 = 10.5 mm. or greater, the ratio R/S in V_5 or V_6 of 1 or less and the ratio R/S in V_1 greater than 1 occurred three times each. An R wave in a V/R of 5 mm. or greater was present only once, and no electrocardiogram showed an R in V_1 of 7 mm. or greater. Comparison with the criteria of Myers, Klein and Stofer was more difficult since the latter are in general rather than in specific terms. Our interpretation of their criteria allows the diagnosis of right ventricular hypertrophy to be made in only three cases. Abnormal P waves were present in two cases, and changes in the standard leads suggestive of right ventricular hypertrophy were present in five cases. All cases diagnosed as right ventricular hypertrophy by the criteria of Myers and his coworkers, all cases showing abnormal "P" waves, and all except one case showing changes in the standard limb leads presumptive of right ventricular hypertrophy were diagnosed by the criteria of Sokolow and Lyon.

Our study showed electrocardiographic evidence of right ventricular hypertrophy in only five of 22 cases, using Sokolow and Lyon's criteria,[6] and, using Myers, Klein and Stofer's criteria,[4] in only 3 of 22 cases. This is a surprisingly low incidence, especially in a group showing isolated right ventricular enlargement.

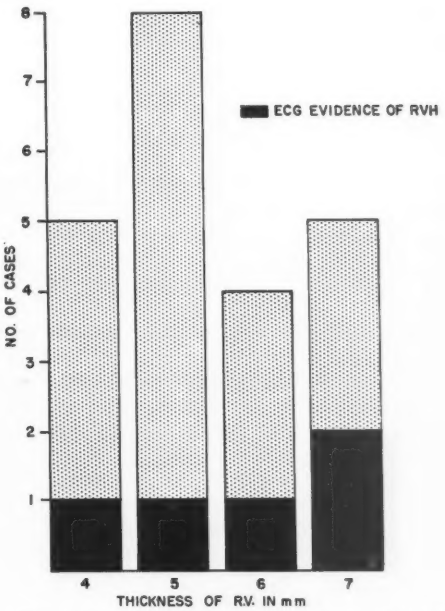


FIG. 3. Result of anatomic–electrocardiographic correlation presented according to thickness of right ventricle.

Table 2 shows that five patients had rheumatic heart disease. Mitral insufficiency was the predominant lesion in one. Of the other four, three showed precordial-lead evidence of right ventricular hypertrophy by the criteria of Sokolow and Lyon, and the fourth showed standard lead changes suggestive of right ventricular hypertrophy. One patient with multiple congenital cardiovascular defects showed electrocardiographic evidence of right ventricular hypertrophy by the criteria of Sokolow and Lyon and incomplete right bundle-branch block by the criteria of Myers and associates. At autopsy 16 patients failed to show diseases such as rheumatic heart disease, cor pulmonale and congenital heart disease, usually associated with right ventricular hypertrophy. Six of these had systemic hypertension. Several had mild emphysema, but in only one case was it marked. Out of this group of 16 cases, only one fulfilled the criteria of Sokolow and Lyon for right ventricular hypertrophy. The etiology of right ventricular enlargement in these patients is not clear. There should be no difference in the frequency

of electrocardiographic changes of right ventricular hypertrophy regardless of the etiology if increase in right ventricular muscle mass alone is the predominant factor in the electrocardiographic pattern of right ventricular hypertrophy. Our findings suggest that other factors, in addition to the actual muscle mass of the right ventricle, may play a role. Four of five patients with electrocardiographic evidence of right ventricular hypertrophy had diseases usually associated with increased pulmonary artery and right ventricular pressures.

Most of the series reported have been restricted to diseases associated with increased pulmonary artery or right ventricular pressures.[1, 2, 4, 6, 7] Johnson and co-workers[15] found that all patients except one with electrocardiographic evidence of right ventricular hypertrophy had a pulmonary artery mean pressure greater than 30 mm. Hg at rest and that 8 of 14 patients with a pulmonary artery mean pressure at rest of greater than 30 mm. Hg showed electrocardiographic evidence of right ventricular hypertrophy. Cosby and his colleagues[16] have demonstrated similar findings. It has been pointed out also that if the level of total pulmonary resistance is 1000 dyne-seconds cm.$^{-5}$ or greater in cases of pure mitral stenosis the electrocardiogram will usually show the pattern of right ventricular hypertrophy.[17, 18]

It has been suggested that rotation may play a role. Kossmann and his associates[19] stated that it is doubtful if hypertrophy alone, except rarely, can cause right axis deviation. They believe that the dominant effect is a

TABLE 1.—*Analysis of Electrocardiogram from Cases Showing Isolated Right Ventricular Hypertrophy at Autopsy*

Pt.	Age	Sex	Heart Wt.	Thickness in mm.		QRS Axis	Lead I					Lead III					aV_R		V_1							Int. Def. in sec.
				RV	LV		Amp. in mm.				R S	Amp. in mm.				R S	Amplitude in mm.		Amplitude in mm.						R S	
							R	S	ST	T		R	S	ST	T		R	T	Q	R	S	R'	ST	T		
M.H.	47	F	315	7	11	115	1.5	6	—*	—	.25	12	0	−1	±		1	—	0	6	2	0	?	?	3	.04
W.S.	75	M	400	5	10	10	7	0	−.5*	—		0	2	—	1		0	.5	0	.5	12	0	—	1	.04	.01
A.H.	51	M	410	7	12	105	0	2.5	—*	1		9	3	−2	±	3	3.5	−1	4	3.5	0	0	.5	1		.05
E.S.	58	M	325	5	12	60	6	0	—*	1		4	0	.5	2		0	−2	0	1	9	0	—	.5	.1	.02
E.G.	65	F	450	5	13	330	18	0	−.5	±		0	16	.5	3		0	1	0	5.5	11	0	—	5	.5	.01
W.R.	35	M	425	5	12	60	5	0	?	?		6	0	?	?		0	?	0	1	9	0	—	±	.1	.02
P.H.	77	M	350	4	13	50	7	0	—	±		3	0	—	1		0	−.5	0	2	6	0	—	2	.33	.02
J.B.	48	M	485	5	12	95	2	2	—	1	1	8	0	—	±		1	−1	0	6	0	0	?	?		.03
D.C.	65	F	367	5	10	45	5	1	−.5	±	5	1	0	—	−1		.5	−.5	0	.5	4	0	—	−1	.12	.01
J.G.	70	M	380	6	12	330	2.5	0	—	—		1	4	—	.5	.25	.5	−.5	10	0	0	0	.5	.5		
R.W.	15	M	?	4-6	10	90	4	4.5	—	—	.9	8	.5	1	3	16	6	—	0	1	5	3.5	—	±	.9	.04
C.R.	76	M	355	5	12	60	12	0	—	1.5		9	0	−.5	1		.5	−2	0	2	14	0	—	1	.14	.02
L.D.	63	F	500	4	12	30	5	0	—	−.5		.5	1.5	—	.25	.3	.5	.5	0	Emb	7	0	—	.25		.01
D.D.	63	M	500	4	10-13	75	4	2	—	.5	2	2	0	—	1		3	1	0	.5	5	0	—	—	.1	.02
A.G.	39	M	365	4	7	60	6	3	—	1	2	4	1	—	?	4	2	−1	0	1	3	0	—	—	.3	.02
A.B.	66	F	675	4	10	105	1	3	—	1	.3	0	0	—	—		3.5	−1	0	1.5	5	0	—	1	.3	.01
M.K.	44	F	475	7	12	105	1.5	3.5	—	−.5	.4	10	0	—	1.5		1.5	—	0	1	4	0	?	?	.25	.02
O.B.	49	F	490	7	13	90	1	0	—	—		2	0	—	±		0	—	0	1	5	0	—	.5	.2	.02
J.F.	79	M	610	6	9	330	7.5	0	−1	±		1	12	—	1	.08	2	±	21	0	0	0	—	4	—	—
L.L.	72	M	495	7	12	60	5	0	−.5	2		1.5	2	—	2	.75	0	−2	0	6	12	0	1	6	.5	.02
H.H.	58	M	450	5	13	60	6	0	—	1		5	2	?	?	2.5	0	−2	0	1	10	0	—	1	.1	.01
E.W.	53	M	380	6	12	330	5	0	—	±		2	7	—	±	.3	2	—	0	1	11	0	±	—	.1	.0

* Minus sign before a numeral indicates depression of the S-T segment or negative T wave. Minus sign without numeral indicates iso-electric S-T segment or flat T wave. Numeral without preceding minus sign indicates elevation of the S-T segment or positive T waves.

Pt.	V_2 Amplitude in mm.						Int. Def. in sec.	Trans. Zone	V_5 Amplitude in mm.					V_6 Amplitude in mm.					Ratio $\frac{R}{S}$ V_{5-6}	$R_{V_1} + S_{V_{5-6}}$ in mm.	Ratio $\frac{\frac{R}{S} V_5}{\frac{R}{S} V_1}$	Elect. Pos. Heart
	Q	R	S	R′	ST	T			Q	R	S	ST	T	Q	R	S	ST	T				
E.H.	0	12		11	0	−1	2	.03	V_{2-4}	0	10	6	—	±	0	8	1	−2	±	1.7	12	.56	Vert.
V.S.	0	1.5		8	0	—	1	.01	V_4	0	13	4	−1	−2	0	10	0	−2	—	3.2	4.5	81	Semi-horiz.
A.H.	0	Emb		16	0	1	4	?	Not Pres.	0	Emb	7	—	1	0	Emb	5	—	1	<1	10.5	.03	Vert.
L.S.	0	5		1	0	—	3	.02	V_{1-2}	.5	14	0	1	3	.5	12	0	1	4		1	140	Semi-vert.
L.G.	0	16		8	0	—	7	.035	V_2	0	16	0	—	3	0	13	0	—	3		5.5	32	Horiz.
W.R.	0	3		15	0	—	6	.02	V_{3-4}	.5	18	0	?	3	.5	13	0	—	2		1	180	Semi-vert.
P.H.	0	5		2	0	—	2.5	.02	V_2	0	20	0	—	2	0	21	0	—	2		2	70	Semi-vert.
J.B.	0	12		5	0	−1	±	.03	V_{2-6}	0	6	8	—	3	0	4	8	—	2	.75	14	.12	Vert.
D.C.	0	3		7	0	—	±	.01	V_3	0	16	5	−1	±	0	14	2	−1	±	3.2	5.5	27	Inter.
J.G.	30	0		0	0	2	5		V_5	6	5	0	—	2	1	11	0	—	±				Horiz.
R.W.	0	5		21	0	—	−2	.02	V_{4-5}	2	43	3.5	—	2	2	33	3	—	3	11	7	11	Vert.
C.R.	0	6		21	0	—	6	.02	V_{2-3}	1	27	0	—	4	0	18	0	−.5	2		2	200	Semi-vert.
L.D.	0	1		10	0	.5	±	.02	V_{4-5}	0	15	2.5	−.5	±	0	9	0	−.5	−.5	7	2.5	45	Inter.
D.D.	0	2		8	0	—	1	.03	V_4	0	9	4	—	1.5	0	5	1	—	1.5	2	4.5	20	Semi-vert.
A.G.	0	6		14	0	1	5	.03	V_4	0	17	5	—	2	0	9	3	—	1	3	6	10	Semi-vert.
A.B.	0	5		12	0	—	−4	.02	V_6	0	7	11	—	−3	0	6	5	—	−1	.63	12.5	2	Vert.
M.K.	0	2.5		16	0	—	2.5	.02	V_{3-4}	0	17	3	−2	±	0	11	1	−.5	±	5.7	4	23	Vert.
O.B.	0	4		16	0	—	2	.01	V_{4-5}	0	5	0	—	−1	0	5	0	—	±		1	25	Semi-vert.
J.F.	25	0		0	0	—	7	—	V_4	0	14	3	−2	±	0	12	2	−1	±	4.7	3		Horiz.
L.L.	0	12		16	0	—	9	.03	V_3	0	10	2	−1	4	0	6	0	—	3	5	8	10	Inter.
H.H.	0	6		8	0	1	6	.02	V_3	0	6	0	−.5	2	0	7	0	−.5	3		1	70	Inter.
E.W.	0	3		17	0	—	−4	.02	V_3	0	16	3	—	—	0	13	2	—	3	5.3	4	55	Horiz.

change in the position of the heart. Goldberger[20] also stated that clockwise rotation can give similar findings. McGregor[21] reported 10 cases of tetralogy of Fallot with electrocardiographic evidence of right ventricular hypertrophy in whom direct leads recorded during thoracotomy showed an rS pattern over the right ventricle and a qR pattern over the left ventricle as in health. He concluded that the rS pattern over the left precordium was due to rotation, the lead actually being taken over the right ventricle. The origin of the R over the right chest was uncertain but he thought it was also due to rotation. Carouso and associates[22] explored with epicardial leads the right and left ventricles of four patients whose electrocardiograms showed right ventricular hypertrophy and failed to confirm McGregor's findings. They found good correlation between right-sided precordial leads and right ventricular epicardial leads as well as between left-sided precordial leads and left ventricular epicardial leads. On the basis of their findings with intracardiac leads Fowler and his co-workers[23] suggested that, in some patients with right ventricular hypertrophy, the qR pattern over the right ventricle may be due to abnormal depolarization of the septum rather than to rotation.

Summary and Conclusions

The electrocardiograms of 22 cases of anatomically proven isolated right ventricular hypertrophy were studied and the findings compared with various electrocardiographic criteria for the diagnosis of right ventricular

TABLE 2.—*Comparison of Electrocardiographic Findings in Patients Showing Isolated Right Ventricular Hypertrophy with Criteria for Electrocardiographic Diagnosis of Right Ventricular Hypertrophy*

Pt.	Criteria for RVH by Sokolow and Lyons												Criteria for RVH by Myers																	
													Group A						Group B	Group C	Group D				Group E		Criteria for RVH Stand. Leads
	R_{V_1} 7 mm. or ↑	S_{V_1} ↓ 2 mm.	$S_{V_{5-6}}$ 7 mm. or ↑	$R_{V_1} + S_{V_{5-6}}$ ↑ 10.5 mm.	$R_{V_{5-6}}$ ↓ 5 mm.	$\frac{R}{S}$ V_{5-6} ↓ or ↓	R_{aVR} 5 mm. or ↑	$\frac{R}{S}$ $V_5 / \frac{R}{S}$ $V_1 = 0.4$ ↓	$\frac{R}{S}$ V_1 ↑ 1	Intr. Defl. V_1 ↑ 0.04 sec.	Inv. $T_{V_{1-3}}$ with R = 5 mm. or ↑	RAD 110°	1	2	3	4	5	6			1	2	3	4		P wave ↑ 3 mm.	
M.H.	0	0	0	0	0	0	0	0	+	+	?	+	0	0	0	0	+	+	—	0	0	0	+	+	0	0	+
W.S.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+	+	—	0	0	0	+	+	0	0	0
A.H.	0	+	+	+	+	+	0	+	+	+	0	0	+	+	+	0	+	+	—	0	0	+	+	0	0	+	+
E.S.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+	+	—	0	0	0	+	+	0	0	0
E.G.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+	+	—	0	0	0	+	+	0	0	0
W.R.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+	+	+	—	0	0	0	+	+	0	AF	0
P.H.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+	+	—	0	0	0	+	+	0	0	0
J.B.	0	+	+	+	+	+	0	+	+	0	?	0	+	+	0	?	+	+	—	0	0	0	+	+	0	+	+
D.C.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+	+	—	0	0	0	+	+	0	0	0
J.G.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+	0	+	+	—	0	0	0	+	0	0	0	0
R.W.	0	0	0	0	0	0	+	0	0	+	+ V2	0	0	+	0	0	+	0	—	0	±	0	+	+	0	0	0
C.R.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+	+	—	0	0	0	+	+	0	0	0
L.D.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+	+	—	0	0	0	+	+	0	0	0
D.D.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+	+	+	—	0	0	0	+	+	0	0	0
A.G.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+	+	—	0	0	0	+	+	0	0	0
A.B.	0	0	+	+	0	+	0	0	0	0	+ V2	±	0	0	0	0	+	+	—	0	0	0	+	+	0	0	+
M.K.	0	0	0	0	0	0	0	0	0	0	0	±	0	0	0	0	+	+	—	0	0	0	+	+	0	AF	+
O.B.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+	+	—	0	0	0	+	+	0	0	0
J.F.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+	0	+	+	—	0	0	0	+	0	0	0	0
L.L.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+	+	—	0	0	0	+	+	0	0	0
H.H.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+	+	—	0	0	0	+	+	0	0	0
E.W.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+	+	—	0	0	0	+	+	0	0	0
Total	0	2	3	3	2	3	1	2	3	3	2	3	2	3	3	2			—	0	1	1			0	2	5

hypertrophy. Five of the 22 had at least one positive criterion of Sokolow and Lyon, and only 3 of the 22 fulfilled the criteria of Myers and his coworkers. Age, heart weight, and the ratio of the right ventricular to the left ventricular thickness did not appear to influence the frequency of positive findings. It appeared that electrocardiographic evidence of right ventricular hypertrophy occurred more frequently as the thickness of the right ventricle increased. Of the five patients showing electrocardiographic evidence of right ventricular hypertrophy, four had diseases usually associated with increased pulmonary artery and right ventricular pressures. Only 1 of the 16 cases having diseases not usually

associated with increased pulmonary artery and right ventricular pressures demonstrated right ventricular hypertrophy electrocardiographically. It is suggested that factors such as increased pressure in the right side of the heart and in the pulmonary circuit, increased total pulmonary resistance, abnormal depolarization in the septum, and possibly rotation, in addition to increased muscle mass of the right ventricle, may contribute to the electrocardiographic pattern of right ventricular hypertrophy. Frequently the electrocardiogram will not be diagnostic in the presence of anatomic right ventricular hypertrophy.

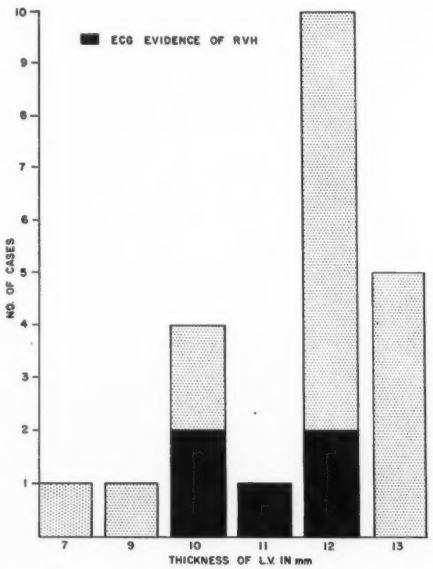


FIG. 4. Result of anatomic-electrocardiographic correlation presented according to thickness of left ventricle.

SUMMARIO E CONCLUSIONES IN INTERLINGUA

Esseva studiate le electrocardiogrammas de 22 anatomicamente demonstrate casos de isolate hypertrophia dexteroventricular. Le constatationes assi facite esseva relationate con le varie criterios electrocardiographic que es currentemente in uso in le diagnose de hypertrophia dexteroventricular. Cinque inter le 22 casos exhibiva al minus un del criterios positive de Sokolow e Lyon; solo 3 satisfaceva le criterios de Myers e su collaboratores. Il pareva que le frequentia de constatationes positive non esseva influentiate per le etate del patiente, le peso del corde, e le proportion inter le spissitates dextero- e sinistro-ventricular. Le frequentia de indices electrocardiogrraphi de hypertrophia dexteroventricular accescevac apparentemente con le spissitate del ventriculo dextere. Inter le cinque patientes exhibiente indices electrocardiographic de hypertrophia dexteroventricular, quatro habeva morbos que es normalmente associate con augmentate pressiones del arteria pulmonar e del ventriculo dextere. Un sol caso inter le 16 casos de morbos non usualmente associate con augmentate pressiones del arteria pulmonar e del ventriculo dextere exhibiva in su electrocardiogramma indices de hypertrophia dexteroventricular. Nos opina que le configuration electrocardiographic de hypertrophia dexteroventricular es possibilemente determinate—ultra le recognoscite effectos del augmentate massa muscular del ventriculo dextere—etiam per factores como le altiate pression in le latere

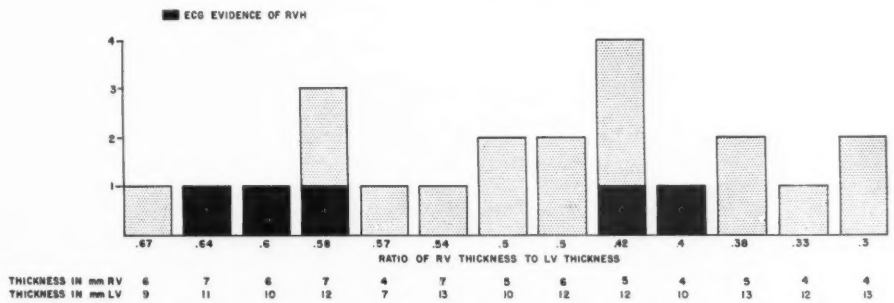

ECG EVIDENCE OF RVH
.67 .64 .6 .58 .57 .54 .5 .5 .42 .4 .38 .33 .3
RATIO OF RV THICKNESS TO LV THICKNESS
THICKNESS IN mm RV 6 7 6 7 4 7 5 6 5 4 5 4 4
THICKNESS IN mm LV 9 11 10 12 7 13 10 12 12 10 13 12 13

FIG. 5. Result of anatomic–electrographic correlation presented according to right ventricular–left ventricular thickness.

dextere del corde e in le circuito pulmonar, un augmentate resistentia pulmonar total, un depolarisation anormal in le septo, e le rotation que occurre in certe casos. In casos de anatomicamente evidente hypertrophia dexteroventricular le electrocardiogramma es frequentemente non-diagnostic.

REFERENCES

[1] Zimmerman, H. A., and Ryan, J. M.: Cor pulmonale: A report of an additional fifty-two cases compared with a previous study of fifty cases. Dis. Chest **20:** 286, 1951.

[2] Spain, D. M., and Handler, B. J.: Chronic cor pulmonale: Sixty cases studied at necropsy. Arch. Int. Med. **77:** 37, 1946.

[3] Sussman, M. L., Grishman, A., and Steinberg, M. F.: The roentgenologic diagnosis of right-sided enlargement of the heart. New England J. Med. **228:** 777, 1943.

[4] Myers, G. B., Klein, H. A., and Stofer, B. E.: The electrocardiographic diagnosis of right ventricular hypertrophy. Am. Heart J. **35:** 1. 1948.

[5] Levine, H. D., and Phillips, E.: An appraisal of the newer electrocardiography: Correlations in one-hundred-and-fifty consecutive autopsied cases. New England J. Med. **245:** 833, 1951.

[6] Sokolow, M., and Lyon, T. P.: The ventricular complex in right ventricular hypertrophy as obtained by unipolar precordial and limb leads. Am. Heart J. **38:** 273, 1949.

[7] Berliner, K., and Master, A. M.: Mitral stenosis: A correlation of electrocardiographic and pathologic observations. Arch. Int. Med. **61:** 39, 1938.

[8] Katz, L. N., Goldman, A. M., Langendorf, R., Kaplan, L. G., and Killian, S. T.: The diagnostic value of the electrocardiogram based on an analysis of 149 autopsy cases. Am. Heart J. **24:** 627, 1942.

[9] —, Feldman, D., and Langendorf, R.: The diagnostic value of electrocardiographic patterns based on an assay of 261 additional autopsied cases. Am. Heart J. **33:** 696, 1947.

[10] Lipsett, M. B., and Zinn, W. J.: Anatomic and electrocardiographic correlation in combined ventricular hypertrophy. Am. Heart J. **45:** 86, 1953.

[11] Zeek, P. M.: Heart weight 1. The weight of the normal human heart. Arch. Path. **34:** 820, 1942.

[12] Scott, R. W., and Garvin, C. F.: Cor pulmonale: Observations in fifty autopsy cases. Am. Heart J. **22:** 56, 1941.

[13] Spatt, S. D., and Grayzel, D. M.: Cor pulmonale: Observations on forty-two autopsied patients. Am. J. Med. **5:** 252, 1948.

[14] Kaufman, J., and Scott, R. C.: Pathologic and electrocardiographic study of the auricles. J. Lab. & Clin. Med. **34:** 1617, 1949.

[15] Johnson, J. B., Ferrer, M. I., West, J. R., and Cournand, A.: The relation between electrocardiographic evidence of right ventricular hypertrophy and pulmonary arterial pressure in patients with chronic pulmonary disease. Circulation **1:** 536, 1950.

[16] Cosby, R. S., Levinson, D. C., Dimitroff, S. P., O'Blath, R. W., Herman, L. M., and Griffith, G. C.: The electrocardiogram in congenital heart disease and mitral stenosis: A correlation of electrocardiographic patterns with right ventricular pressure, flow, and work. Am. Heart J. **46:** 670, 1953.

[17] Scott, R. C., and Kaplan, S.: The electrocardiogram in mitral valve disease. J. Lab. & Clin. Med. **42:** 950, 1953.

[18] Lewis, B. M., Gorlin, R., Houssay, H. E. J., Haynes, F. W., and Dexter, L.: Clinical and physiological correlations in patients with mitral stenosis. V. Am. Heart J. **43:** 2, 1952.

[19] Kossmann, C. E., Berger, A. R., Brumlik, J., and Briller, S. A.: An analysis of causes of right axis deviation based partly on endocardial potentials of the hypertrophied right ventricle. Am. Heart J. **35:** 309, 1948.

[20] Goldberger, E.: Effects of clockwise rotation of the heart on the electrocardiogram. Am. J. Med. **7:** 756, 1949.

[21] McGregor, M.: The genesis of the electrocardiogram of right ventricular hypertrophy. Brit. Heart J. **12:** 351, 1950.

[22] Carouso, G. J., Chevalier, H. A., Latscha, I. B., and Lenegre, J.: Epicardial electrocardiograms recorded in the course of seven cases of heart surgery. Circulation **5:** 48, 1952.

[23] Fowler, N. O., Jr., Westcott, R. N., and Scott, R. C.: The Q wave in precordial electrocardiograms overlying the hypertrophied right ventricle: intracavity leads. Circulation **5:** 441, 1952.

Right Ventricular Hypertrophy

II. Correlation of Electrocardiographic Right Ventricular Hypertrophy with the Anatomic Findings

By Isom C. Walker, Jr., M.D., Ralph C. Scott, M.D., and Robert A. Helm, M.D.

Twelve cases whose electrocardiograms fulfilled at least one criterion of Sokolow and Lyon for right ventricular hypertrophy were examined at autopsy. Eight of the 12 demonstrated right ventricular hypertrophy anatomically. Eleven of the 12 cases had diseases usually associated with increased pressure in the right ventricle and pulmonary artery and with increased total pulmonary resistance. It is likely that factors other than muscle mass contribute significantly to the electrocardiographic pattern of right ventricular hypertrophy.

In a previous study from this laboratory, cases showing isolated right ventricular hypertrophy at autopsy were studied to determine the frequency of concomitant electrocardiographic evidence of right ventricular hypertrophy.[1] The correlation was surprisingly poor. Using the criteria of Sokolow and Lyon,[2] only 5 of 22 cases, with isolated right ventricular enlargement at autopsy, could have been diagnosed from the electrocardiogram. Only 3 of the 22 cases fulfilled the criteria of Myers and co-workers.[3] The present study was undertaken to determine the reliability of electrocardiograms demonstrating the pattern of right ventricular hypertrophy. Other authors have stated that if the electrocardiogram shows the pattern of right ventricular hypertrophy, this diagnosis will be substantiated at autopsy. Sokolow and Lyon[2] found anatomic confirmation in 17 of 18 instances when their criteria for right ventricular hypertrophy were used. Levine and Phillips[4] reported correlation in eight of eight cases of right ventricular hypertrophy. Katz and his colleagues[5] reported correlation in seven of eight cases.

Method

Electrocardiographic records fulfilling at least one criterion suggested by Sokolow and Lyon[2] were studied. Those showing an R′ in V_1 or a delay in the onset of the intrinsicoid deflection in V_1 of greater than 0.05 second or other criteria of incomplete right bundle-branch block, or complete right bundle-branch block were excluded from the study, although, as demonstrated by Myers and his associates,[3] these findings often connote anatomic right ventricular hypertrophy. Twelve adult cases who fulfilled the above criteria and who had had an autopsy, including a determination of heart weight and ventricular wall thicknesses were included in this study. This survey covered a period of five years. The criteria for anatomic right ventricular hypertrophy were heart weight exceeding the mean standard deviation from normal for body weight[6] and a right ventricular thickness of 5 mm. or more[7–10] or of 4 mm. in the presence of dilatation.[1]

Results

Table 1 shows the analysis of the electrocardiograms of the 12 cases studied. Five of the 12 had a Q wave in V_1. Table 2 demonstrates the comparison of these findings with criteria of Sokolow and Lyon,[2] of Myers and colleagues[3]* abnormal "P" waves[11] and stand-

From the Cardiac Laboratory, Cincinnati General Hospital, and the Department of Internal Medicine, College of Medicine, University of Cincinnati, Cincinnati, Ohio.

Dr. Helm is a Public Health Service Research Fellow of the National Heart Institute.

* Myers, Klein and Stofer's criteria for right ventricular hypertrophy:

A. Pattern of right ventricular hypertrophy in leads V_1 to V_6. (1) Reversal in ratio of the amplitudes of the R and S waves in V_1 and V_6 characterized by an abnormally large R in proportion to S in V_1, a diminution in ratio in leads further to the left and a prominent S in V_6. (2) Time interval from beginning of QRS to onset of intrinsicoid deflection that was abnormally long in V_1 and greater than in V_5 or V_6. (3) Tendency to a small Q wave in V_1. (4) Tendency to inversion of the T wave in V_1, and to upright T wave in V_6. (5) Total duration of QRS less than 0.12 second and generally within the normal range. (6)

TABLE 1.—*Analysis of Electrocardiograms Showing Right Ventricular Hypertrophy*

Pt.	Age	Sex	Heart Wt.	Thickness in mm.		QRS Axis	Lead I					Lead III					aV_R		V_1							Int. Def. in Sec.
							Amp. in mm.				R/S	Amp. in mm.				R/S	Amp. in mm.		Amp. in mm.						R/S	
				RV	LV		R	S	ST	T		R	S	ST	T		R	T	Q	R	S	R′	ST	T		
C.C.	47	M	325*	5-8	13	120	.5	3	—	—	.17	3	0	−.5	—		2.5	−.5	.5	4	0	0	—	—		.03
M.C.	35	F	295	3	12	120	0	2	—	—		8	3	—	1	2.7	1	−1	0	5	0	0	?	?		.03
D.K.	30	M	850	17-21	15-17	130	4	20	—	2	.2	18	0	—	−2		8	−2	6	28	0	0	—	−7		.05
M.H.	47	F	315	7	11	115	1.5	6	—	—	.25	12	0	−1	—		1	—	0	6	2	0	?	?	3	.04
J.I.	68	M	300*	4	17	330	3	.5	—	—	6	1	6	—	1	.17	1.5	−.5	0	2	1	0	—	−2	2	.02
J.W.	37	M	487	5	15	120	1	3	—	.5	.3	7	0	−1	—		0	−1	2	1	0	0	—	—		.04
C.M.	51	M	440	5	11	120	2	4	—	1	.5	12	0	—	1		4	−2	0	1	4	0	−1	−3	.25	.02
J.P.	71	M	215*	2	11	0	3	0	—	1		2	3	—	1.5	.67	1	−1	0	2	0	0	—	−.5		.02
G.P.	42	M	385	5-10	15	130	.5	4	—	.5	.12	2	0	−1	−1		3	−.5	1	4	0	0	—	−.5		.04
A.H.	51	M	410	7	12	105	0	2.5	—	1		9	3	−2	—	3	3.5	−1	4	3.5	0	0	.5	1		.05
J.B.	48	M	485	5	12	95	2	2	—	1	1	8	0	—	—		1	−1	0	6	0	0	?	?		.03
A.B.	66	F	675	4	10	105	1	3	—	1	.33	9	0	—	—		3.5	−1	0	1.5	5	0	—	1	.3	.01

	V_2							Int. Def. in Sec.	Trans. Zone	V_5					V_6					R/S Ratio V_{5-6}	$R_{V_1} + S_{V_{5-6}}$ in mm.	Ratio $\frac{R/S\ V_5}{R/S\ V_1}$	Elect Pos. Heart
	Amp. in mm.									Amp. in mm.					Amp. in mm.							
	Q	R	S	R′	ST	T				Q	R	S	ST	T	Q	R	S	ST	T				
C.C.	.5	3	4	0	?	?	.04	Not pres.		0	3	13	—	2	0	4	10	?	?	.4	17	.05	Vert.
M.C.	0	6	6	0	−.5	2	.02	V_4		0	8	3	—	3	0	6	2	—	2	2.7	8	.54	Indeter.
D.K.	2	7	19	0	—	−4	.03	Not pres.		0	7	14	—	1	0	6	12	—	2	.5	42	.02	Vert.
M.H.	0	12	11	0	−1	2	.03	V_{2-4}		0	10	6	—	—	0	8	1	−2	—	1.7	12	.56	Vert.
J.I.	0	5	3	0	0	−1	.03	V_{2-3}		1	20	3	−.5	—	.5	12	1	—	—	6.7	5	3.4	Horiz.
J.W.	1	0	0	0	—	—		Not pres.		.5	9	8	1	3	0	10	6	—	1	1.1	9	1.1	Vert.
C.M.	0	4	24	0	−1	−3	.02	V_5		.5	9	5	—	2	1	8	2	—	1.5	1.8	6	7	Vert.
J.P.	0	4	1	0	—	1	.03	Not pres.		0	8	.5	—	2	.5	6	1	—	2	6	3	8	Vert.
G.P.	.5	3	5	0	−1	1	.03	V_6		0	6	12	—	1	0	2	2.5	—	1.5	.5	16	.12	Indeter.
A.H.	0	Emb	16	0	1	4	?	Not pres.		0	Emb	7	—	1	0	Emb	5	—	1	<1	10.5	.03	Vert.
J.B.	0	12	5	0	−1	—	.03	V_{2-6}		0	6	8	—	3	0	4	8	—	2	.75	14	.12	Vert.
A.B.	0	5	12	0	—	−4	.02	V_6		0	7	11	—	−3	0	6	5	—	−1	.63	12.5	2	Vert.

* Normal heart weight.

TABLE 2.—*Comparison of Electrocardiographic Findings with Criteria for Right Ventricular Hypertrophy*

Pt.	Criteria for RVH by Sokolow and Lyons												Criteria for RVH by Myers																							
													Group A						Group B	Group C	Group D				Group E											
	R_{V_1} 7 mm. ↑	S_{V_1} ↓ 2 mm.	$S_{V_{5-6}}$ 7 mm. ↑	$R_{V_1} + S_{V_{5-6}}$ ↑ 10.5 mm.	$R_{V_{5-6}}$ ↓ 5 mm.	$\frac{R}{S}$ V_{5-6} 1 or ↓	R_{aV_R} 5 mm. ↑	$\frac{R}{S}$ $V_5/\frac{R}{S}$ $V_1 = 0.4$ ↓	$\frac{R}{S}$ V_1 ↑ 1	Int. Def. V_1 ↑ .04 sec.	R-ST V_{1-2} R_5 mm. ↑	RaD 110°	1	2	3	4	5	6			1	2	3	4		P Wave ↑ 3 mm.	Criteria for RHV Stand. Leads
C.C.	0	+	+	+	+	+	0	+	+	0	0	+	+	0	+	?	+	+	—	0	0	0	+	0	0	0		+
M.C.	0	+	0	0	0	0	0	0	+	0	0	+	±	0	0	?	+	+	—	0	0	0	+	+	0	AF	+
D.K.	+	+	+	+	0	+	+	+	+	+	+	+	+	+	+	+	+	+	—	0	0	±	+	0	0	+	+
M.H.	0	±	0	+	0	0	0	0	+	±	0	+	+	±	0	?	+	+	—	0	0	0	+	+	0	0	+
J.I.	0	+	0	0	0	0	0	0	+	0	0	0	±	0	0	?	+	+	—	0	0	0	+	+	0	0	0
J.W.	0	+	+	0	0	0	0	0	+	±	0	+	+	±	+	+	+	+	—	0	0	0	+	0	0	0	+
C.M.	0	0	0	0	0	0	0	0	0	0	0	+	0	0	0	+	+	+	—	0	0	0	+	+	0	0	+
J.P.	0	+	0	0	0	0	0	0	+	0	0	0	0	0	0	±	+	+	—	0	0	0	+	+	0	0	0
G.P.	0	+	+	+	+	+	0	+	+	±	0	+	+	±	+	+	+	+	—	0	0	0	+	0	0	+	+
A.H.	0	+	+	+	+	+	0	+	+	+	0	0	+	+	+	0	+	+	—	0	0	±	+	0	0	+	+
J.B.	0	+	+	+	+	+	0	+	+	0	?	0	+	+	0	?	+	+	—	0	0	0	+	+	0	+	+
A.B.	0	0	+	+	0	+	0	0	0	0	+	±	0	0	0	0	+	+	—	0	0	0	+	+	0	0	+
Total 12	1	9	7	7	4	6	1	5	10	2	2	7	7	3	5	4			—	0	0	0	12	7	0	4	10

ard lead changes suggestive of right ventricular hypertrophy.[12] The majority of the cases fulfilled several criteria. The most frequent finding was an R-S ratio in V_1 greater than unity. This was present in 10 cases. An S in V_1 of less than 2 mm. occurred nine times and an S in V_5 or V_6 of 7 mm. or greater, an R in V_1 + an S in V_5 or V_6 of 10.5 mm. or greater and right axis deviation of 110 degrees or greater were present in seven cases each.

It is interesting to note that an R in V_1 of 7 mm. or greater and an R wave in aV_R of 5 mm. or greater occurred only once each. The onset of the intrinsicoid deflection in V_1 was greater than 0.04 second in only two cases. Four tracings showed abnormal "P" waves.

Eight of the 12 hearts (table 3) had a right ventricular thickness of 5 mm. or greater. Two were 4 mm. in thickness, one was 3 mm. thick and one was 2 mm. thick. Four cases had left ventricular hypertrophy anatomically with a left ventricular thickness of 15 mm. or greater.[13] Three of the hearts did not exceed the mean standard deviation above normal for weight according to the criteria of Zeek.[6] Using the criteria for right ventricular hypertrophy of a right ventricular thickness of 5 mm. or more, or a right ventricular thickness of 4 mm. with dilatation and a heart weight

Absence of notching or double peaking of the R wave in V_1.

B. Pattern of right ventricular hypertrophy or incomplete right bundle-branch block in lead V_{3R} and not in V_1 or V_2.

C. Pattern presumptive of right ventricular hypertrophy in V_6 and aV_R without confirmatory signs in V_1 or V_2.

D. Incomplete right bundle branch block. (1) In leads from right side of precordium, R wave prominent and exhibited either a coarse notch or double peak and S waves small or absent, whereas, in leads further to the left, S wave deeper and broader. (2) Time interval from beginning of QRS to onset of intrinsicoid deflection in V_4 between 0.05 and 0.075 second. (3) Total duration of QRS less than 0.12 second. (4) Absence of Q wave in leads from right precordium.

E. Complete right bundle branch block.

TABLE 3.—*Correlation of Heart Weight and Ventricular Thickness with Pathological Diagnosis*

Pt.	Heart Wt. in Gm.	Ventric. Thickness in mm.		Pathologic Diagnosis
		RV	LV	
1. C.C.	325*	5–8	13	Bronchiectasis
2. M.C.	295	3	12	RHD with mitral Stenosis
3. D.K.	850	17–21	15–17	Patent ductus, anom. left coronary. Severe pulmonary A. S.
4. M.H.	315	7	11	RHD with mitral stenosis
5. J.I.	300*	4	17	Adeno Ca panc. with metast lungs. Acute myocardial infarct
6. J.W.	487	5	15	Emphysema and fibrosis
7. C.M.	440	5	11	Silicosis
8. J.P.	215*	2	11	Bronchogenic Ca RUL, pneumonia, atelectasis and emphysema
9. G.P.	385	5–10	15	Bronchiectasis
10. A.H.	410	7	12	RHD with mitral stenosis
11. J.B.	485	5	12	Calcific mitral stenosis
12. A.B.	675	4	10	Mild coronary sclerosis. Min. emphysema.

* Normal Heart Weight.

exceeding the mean standard deviation above normal,[1] 8 of the 12 cases showed right ventricular hypertrophy at autopsy.

DISCUSSION

Several factors may contribute to the production of the electrocardiographic pattern of right ventricular hypertrophy. These include the actual right ventricular muscle mass, the elevation of pressure in the lesser circulation,[14, 15] the total pulmonary resistance[16] and possibly rotation.[17-19] We have suggested in a previous paper[1] that right ventricular muscle mass alone appears less important than some of the other factors mentioned.

In the present study we have further evidence to support this contention. Four of the 12 cases did not have right ventricular hypertrophy at autopsy despite the presence of electrocardiographic patterns suggesting it. One of these patients had rheumatic heart disease with mitral stenosis. Another had bronchiectasis. A third had adenocarcinoma of the pancreas with metastasis to the lungs. A fourth patient with a bronchogenic carcinoma of the right upper lobe, pneumonia, atelectasis and emphysema, had electrocardiographic evidence of right ventricular hypertrophy although the heart weighed 215 Gm. and the right ventricular thickness was 2 mm. Only one case in this group had no disease of his lungs or heart usually associated with right sided pressure elevation.

SUMMARY AND CONCLUSIONS

1. Twelve cases showing electrocardiographic evidence of right ventricular hypertrophy were examined pathologically for evidence of anatomic right ventricular hypertrophy.

2. Eight of the 12 cases had anatomic right ventricular hypertrophy.

3. Eleven of the 12 cases had disease processes usually associated with increased pressure in the right ventricle and pulmonary artery and increased total pulmonary resistance.

4. If an electrocardiogram shows the pattern of right ventricular hypertrophy, this diagnosis will be confirmed at autopsy in most instances.

5. Further evidence is presented that factors other than increased right ventricular mass contribute to the electrocardiographic pattern of right ventricular hypertrophy.

SUMMARIO IN INTERLINGUA

Dece-duo casos in que le electrocardiogrammas exhibiva indicios de hypertrophia dexteroventricular esseva examinate pathologicamente in re le presentia de indicios anatomic de hypertrophia dexteroventricular. In 8 inter 12 casos, hypertrophia dexteroventricular esseva constatate per medios anatomic. In 11 inter le 12 casos processos morbose esseva manifeste que es normalmente associate con altiate pression del ventriculo dextere e del arteria pulmonar e con augmentate resistentia pulmonar total. In le majoritate del casos de electrocardiogrammas con configurationes de hypertrophia dexteroventricular, on pote expectar que le dignose va esser confirmate per le autopsia. Nos presenta datos additional que supporta le conception que un massa augmentate del ventriculo dextere non es le sol factor determinante in le configuration electrocardiographic de hypertrophia dexteroventricular.

REFERENCES

[1] WALKER, I. C., JR., HELM, R. A., AND SCOTT, R. C.: Right ventricular hypertrophy. I. Correlation of isolated right ventricular hypertrophy at autopsy with the electrocardiographic findings. Circulation. **11:** 215, 1955.

[2] Sokolow, M., and Lyon, T. P.: The ventricular complex in right ventricular hypertrophy as obtained by unipolar precordial and limb leads. Am. Heart J. **38:** 273, 1949.

[3] Myers, G. B., Klein, H. A., and Stofer, B. E.: The electrocardiographic diagnosis of right ventricular hypertrophy. Am. Heart J. **35:** 1, 1948.

[4] Levine, H. D., and Phillips, E.: An appraisal of the newer electrocardiography: Correlations in one-hundred-and-fifty consecutive autopsied cases. New England J. Med. **245:** 833, 1951.

[5] Katz, L. N., Goldman, A. M., Langendorf, R., Kaplan, L. G., and Killian, S. T.: The diagnostic value of the electrocardiogram based on an analysis of 149 autopsy cases. Am. Heart J. **24:** 627, 1942.

[6] Zeek, P. M.: Heart Weight 1. The weight of the normal human heart. Arch. Path. **34:** 820, 1942.

[7] Zimmerman, H. A., and Ryan, J. M.: Cor pulmonale: A report of an additional fifty-two cases compared with a previous study of fifty cases. Dis. Chest **20:** 286, 1951.

[8] Scott, R. W., and Garvin, C. F.: Cor pulmonale: Observations in fifty autopsy cases. Am. Heart J. **22:** 56, 1941.

[9] Spatt, S. D., and Grayzel, D. M.: Cor pulmonale: Observations in forty-two autopsied patients. Am. J. Med. **5:** 252, 1948.

[10] Spain, D. M., and Handler, B. J.: Chronic cor pulmonale: Sixty cases studied at necropsy. Arch. Int. Med. **77:** 37, 1946.

[11] Kaufman, J., and Scott, R. C.: Pathologic and electrocardiographic study of the auricles. J. Lab. & Clin. Med. **34:** 1617, 1949.

[12] Berliner, K., and Master, A. M.: Mitral stenosis: A correlation of electrocardiographic and pathologic observations. Arch. Int. Med. **61:** 39, 1938.

[13] Lipsett, M. B., and Zinn, W. J.: Anatomic and electrocardiographic correlation in combined ventricular hypertrophy. Am. Heart J. **45:** 86, 1953.

[14] Johnson, J. B., Ferrer, M. I., West, J. R., and Cournand, A.: The relation between electrocardiographic evidence of right ventricular hypertrophy and pulmonary arterial pressure in patients with chronic pulmonary disease. Circulation **1:** 536, 1950.

[15] Cosby, R. S., Levinson, D. C., Dimitroff, S. P., O'Blath, R. W., Herman, L. M., and Griffith, G. C.: The electrocardiogram in congenital heart disease and mitral stenosis: A correlation of electrocardiographic patterns with right ventricular pressure, flow, and work. Am. Heart J. **46:** 670, 1953.

[16] Scott, R. C., and Kaplan, S.: The electrocardiogram in mitral valve disease. J. Lab. & Clin. Med. **42:** 950, 1953.

[17] Kossman, C. E., Berger, A. R., Brumlik, J., and Briller, S. A.: An analysis of causes of right axis deviation based partly on endocardial potentials of the hypertrophied right ventricle. Am. Heart J. **35:** 309, 1948.

[18] Goldberger, E.: Effects of clockwise rotation of the heart on the electrocardiogram. Am. J. Med. **7:** 756, 1949.

[19] McGregor, M.: The genesis of the electrocardiogram of right ventricular hypertrophy. Brit. Heart J. **12:** 351, 1950.

Some Observations on the Relation of the High-Frequency Bed Ballistocardiogram to that Obtained from an Aperiodic Bed

By DENNIS C. DEUCHAR, M.D., M.R.C.P., SAMUEL A. TALBOT, PH.D., AND W. R. SCARBOROUGH, M.D.

A previous analysis of the mechanical behavior of current ballistocardiographic systems allowed the prediction of certain relationships between records from the Starr high-frequency bed and those representing undistorted forces applied to the body by the cardiovascular "generator." The latter were obtained by recording the acceleration of an "aperiodic mercury bed" platform. A relationship between the form of these two types of records from 80 subjects was sought. In varying types of normal and abnormal records the predicted relationship between the two different kinds of ballistocardiograms was consistently observed. It is concluded that records from the high-frequency bed grossly reflect the slower forces applied to the body, but are distorted with respect to phase, amplitude and frequency content, this being due in part to the elastic properties of the dorsal surface of the body and in part to the weight and stiffness of the platform support.

AN analysis of the current methods of ballistocardiography has shown that they are all subject to significant imitations and distortions.[1, 2] The most important factor involved relates to the manner in which the human body is supported. With both the high-frequency bed and the direct body methods the body is coupled to and loaded by heavy, relatively rigid platforms or tables. When the body moves in response to internally generated cardiovascular forces, such supporting structures are unable to follow these motions since their weight and rigidity render them relatively immobile. This causes the body to oscillate back and forth on its own soft springs which are formed by the dorsal tissues connecting the body to its supporting surface. As a consequence, the behavior of high frequency bed and direct body systems becomes largely dominated by the elastic properties of the dorsal tissues. This inevitably produces a seriously distorted frequency response in an important part of the ballistocardiographic frequency range. One of the errors introduced is in amplitude response. Those forces applied at frequencies comparable to the body's own natural frequency (4 to 5 cycles per second) are greatly exaggerated in amplitude while those applied at higher frequencies are considerably attenuated. Furthermore, since the human body is underdamped, a single impact applied to it is followed by a series of diminishing oscillations. That this behavior causes distortion of the ballistocardiogram is a fact well recognized by Starr at a very early stage in his work.[3] Another error produced by the dominance of the body's dorsal springs is in phase (or timing) characteristics. Beginning with frequencies well below the body's own natural frequency, the motions of the body (and the high-frequency bed platform) tend to lag behind forces driving the body. This phase lag, which progressively increases as the driving frequency is increased, leads to errors in timing.

We have already published a brief report[4] concerning our attempts to approach the ideal system, as described by Nickerson[5] and Burger and co-workers[6] in which the body would be free of all restoring and damping forces, as if floating in space. With such a system the body's

From the Department of Medicine, The Johns Hopkins School of Medicine and Hospital, Baltimore, Md.

This work was supported (in part) by a grant from the Life Insurance Medical Research Foundation and (in part) by a grant (H-327) from the National Heart Institute, National Institutes of Health, Public Health Service.

Drs. Deuchar and Scarborough are Fellows in Residence, Howard Hughes Foundation.

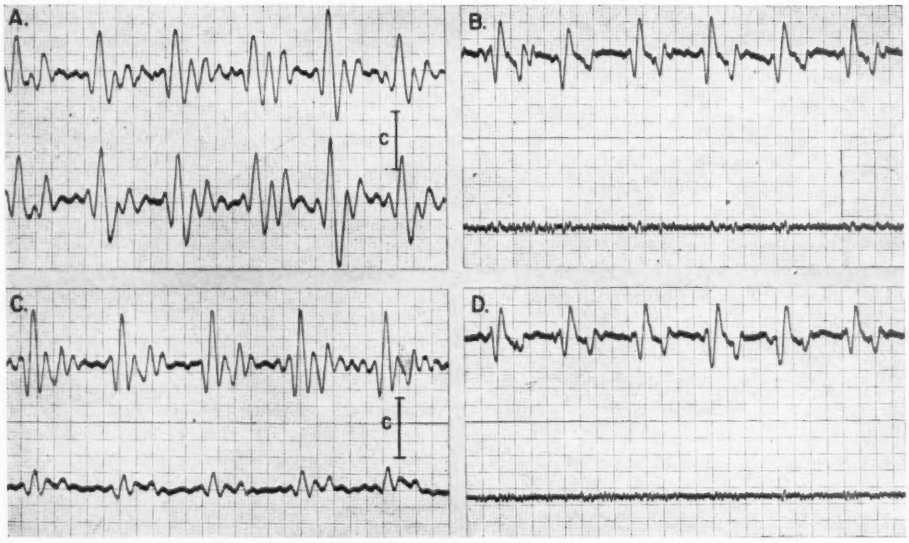


FIG. 1. Four sets of simultaneous recordings of platform motion and relative motion between subject (shins) and platform; in each case the platform record is the upper tracing. The same subject was used for all the tests. The records in *A* and *C* relate to the high-frequency bed while those in *B* and *D* refer to the aperiodic bed. In *C* and *D* the subject's feet were against a footboard; in *A* and *B* they were not.

In *A* and *C* the upper tracing is the usual high-frequency bed record, representing the *displacement* of the platform. The lower tracing is a direct-body record from the shins of the subject lying on the high-frequency bed and represents *displacement* of the body with respect to the platform. The calibration marked "C" corresponds to a displacement of 3.5 microns for the Starr bed record and of 25.0 microns for the direct-body record.

In *B* and *D* the upper tracing is the acceleration record from the aperiodic bed platform and the lower tracing is the acceleration record from the shins referred to the platform. Calibration is the same for both records (1 cm. = approx. 1 cm per second^2).

With the high-frequency bed the displacement of the body is about seven times as great as that of the platform; although the use of a footboard reduces the discrepancy, relative motion remains large. On the other hand, motion of the body with respect to the aperiodic bed platform is so small as to be almost unmeasurable, and this is made even smaller when a footboard is used. For practical purposes, the aperiodic bed platform and the subject on it can be considered to move in unison in response to cardiovascular forces.

acceleration would measure directly the force transmitted to it from the cardiovascular system, assuming a unified body mass. Briefly, our aperiodic ballistocardiography consists of a light platform (weight about 11 pounds) floating on a shallow pool of mercury: such a system has no restoring force, so can be called aperiodic, and has minimal damping. These properties minimize excitation of the dorsal tissues; coupling of the body to platform is further improved by use of a footboard. The relative motion between the body and platform on the high-frequency (Starr) ballistocardiograph is compared with that on the aperiodic (mercury) bed in figure 1. This figure shows the ballistocardiogram as recorded from these systems together with simultaneous "direct body" ballistocardiograms taken from the shins (and referred to the platform) by means of a calibrated ballistocardiographic pickup.*[7]

* D.V.A. ballistocardiograph, manufactured by the Industrial Development Laboratories, Inc., Jersey City, N. J. Displacement is recorded with a differential transformer; although the core is spring-mounted, the spring constant is so small as to be negligible in this application. Acceleration is obtained by differentiating the output of an electromagnetic pickup.

This demonstrates the very small motion between body and platform on the aperiodic bed, even more reduced by the use of the footboard, as compared with the similar motion on the high-frequency bed.

Burger and associates[6] in their analysis of the physical basis of ballistocardiographic systems suggested that the magnitude of the *displacement* of a high-frequency bed platform represents the force acting on the body. In reaching this conclusion, however, they did not take into account all the complexities of the system. The analysis from this department[2] has shown that this suggested relationship is true only for a limited frequency range. This range, however, seems to include the largest forces acting on the body, which are those responsible for the main features of the Starr-type record. We might expect, then, that the gross features of this type of record would give an indication of the major forces applied to the body by the cardiovascular generator.

The analysis previously mentioned[2] enables us to predict certain relationships between the records from the high-frequency bed and those from the aperiodic ballistocardiograph. Taking the latter as the reference record depicting force acting on the body, it is possible to predict that the record from the high-frequency bed will show the following properties: (1) it will show the main forces in the lower frequency range while those of higher frequency will be more or less attenuated and those about the body's natural frequency will be exaggerated; (2) in sections of the record following deflections at the natural frequency of the body it will show waves compounded of freshly impressed forces and after-oscillations excited by the earlier deflection, and (3) it will represent all but the slowest oscillations later in time, a result of the phase shift referred to above.

The work being reported here was undertaken to investigate whether this theoretically predicted relationship could be confirmed in practice.

Methods and Materials

Head-foot records were obtained on both a high-frequency bed and the aperiodic ballistocardiograph. The high-frequency bed was the instrument used in previously reported studies,[8-11] but for this study the records were made using a Sanborn strain gage amplifier and two-channel direct-writing recorder; the second channel was used to record the lead II electrocardiogram. The aperiodic ballistocardiograms were obtained as previously reported,[4] using a 2g Statham accelerometer on the platform with a cathode-follower and the Sanborn amplifier: additional amplification with a direct current amplifier was used to obtain adequate sensitivity and a high-cut filter was incorporated to obtain a response from transducer to pen flat to 40 cycles per second but with attenuation above this level. Sensitivity was adjusted to 5 mm. deflection for one thousandth of g (acceleration due to gravity), roughly 1 cm. per second^2. On both systems records were taken with the subject's feet against the footboard and with the subject breathing normally except for a short period during which the breath was held in midinspiration. The records so obtained were compared to determine the relationship between those from the two systems. It should be kept in mind that the comparison was between the usual *displacement* record from the high frequency bed and the *acceleration* record from the aperiodic bed.

Table 1.—*Analysis of Aperiodic Ballistocardiograms Studied*

Diagnostic classification of subjects	Classification of Records			Totals
	Normal	Borderline	Abnormal	
No evidence of cardiovascular disease	39	7	9	55
Coronary artery disease	3	3	10	16
Other forms of cardiovascular disease	2	1	6	9
Totals	44	11	25	80

Records from 80 subjects have been used for this study; 55 of these had no evidence of cardiovascular disease, 16 had coronary artery disease and nine had other forms of cardiovascular disease. A breakdown of the subjects and records is given in table 1. In this table the term "normal" applied to the character of the aperiodic ballistocardiogram means that the complexes had a form similar to that consistently observed in all young normal subjects. Our experience, previously reported[4] on the basis of 20 subjects, that such a consistent, easily recognizable pattern is obtained from the aperiodic ballistocardiograph has been confirmed in the larger series now under discussion. "Abnormal" records are those which depart from the normal pattern in some clear qualitative fashion; "borderline" is used to described records intermediate between clearly normal or abnormal, for which, at present, our criteria are insufficiently precise to permit certain classification. It should be noted that no statis-

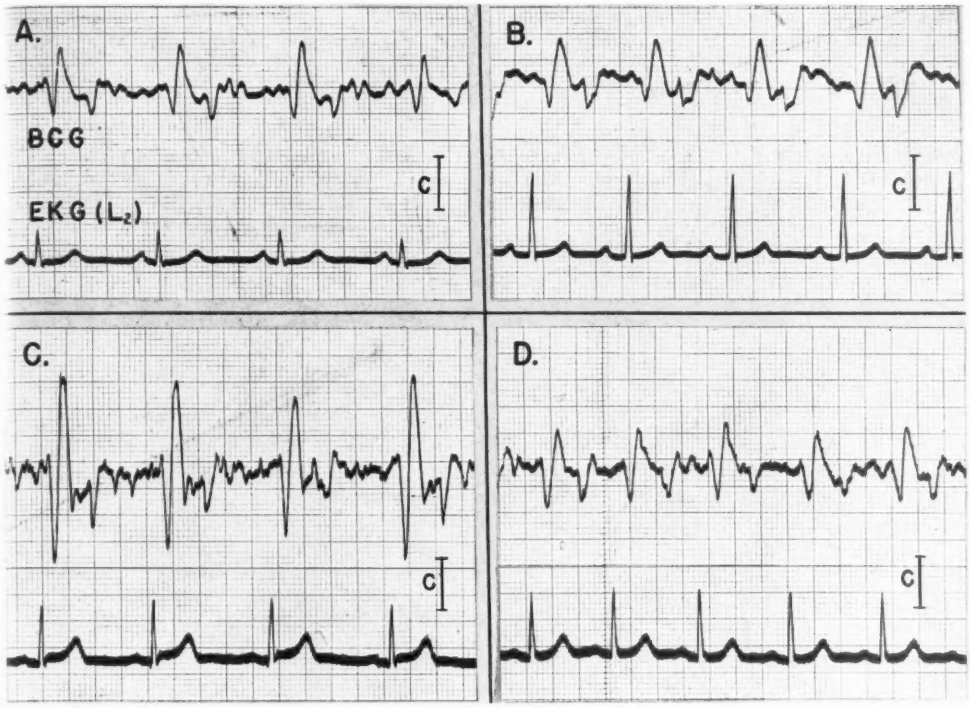


FIG. 2. Typical acceleration records obtained from four young normal subjects on the aperiodic bed, together with the simultaneously recorded electrocardiogram. Note the general resemblance of the form of the records. The calibration, marked "C" on the records, represents the deflection produced by an acceleration of 0.002 g, which would result from the action of a 136 Gm. force on a 150 pound body. (This figure is reproduced here by permission of the Bulletin of the Johns Hopkins Hospital.)

tical significance is claimed for the figures in the table; subjects were selected to provide the variety of records we required. The information is given solely to indicate the nature of the material used.

OBSERVATIONS

Normal Records

Figure 2 shows some typical normal records from the aperiodic ballistocardiograph. The main features of these records[4] are a small headward wave with its tip occurring at a mean interval of 0.09 second after the Q wave in the lead II electrocardiogram, a prominent footward wave with its tip 0.14 second (mean) after the Q wave followed by the main headward deflection with a tip 0.21 second (mean) after the Q*; after this deflection the record is more variable in form, with a slower return to the base line and usually a footward segment of small amplitude but longer duration, often culminating in a sharper footward deflection just before a more uniform headward wave of small amplitude at 0.52 second after the Q wave. Sometimes the last footward deflection referred to is preceded by a well-defined wave approaching the base line but rarely crossing it. (See also figure 12 for a diagrammatic representation of this.)

In figure 3 four examples are shown of enlarged, single complexes from normal records, taken on both systems, superimposed upon each other to illustrate their mutual relationship. By the nature of things it is not possible to record these two types of ballistocardiogram simultaneously, but in the preparation of this and similar figures care has been taken to match complexes with respect to phase of respiration

* These intervals may be compared with previously reported[9] mean values from normal high-frequency bed records: Q-H = 0.10, Q-I = 0.18 and Q-J = 0.25 second.

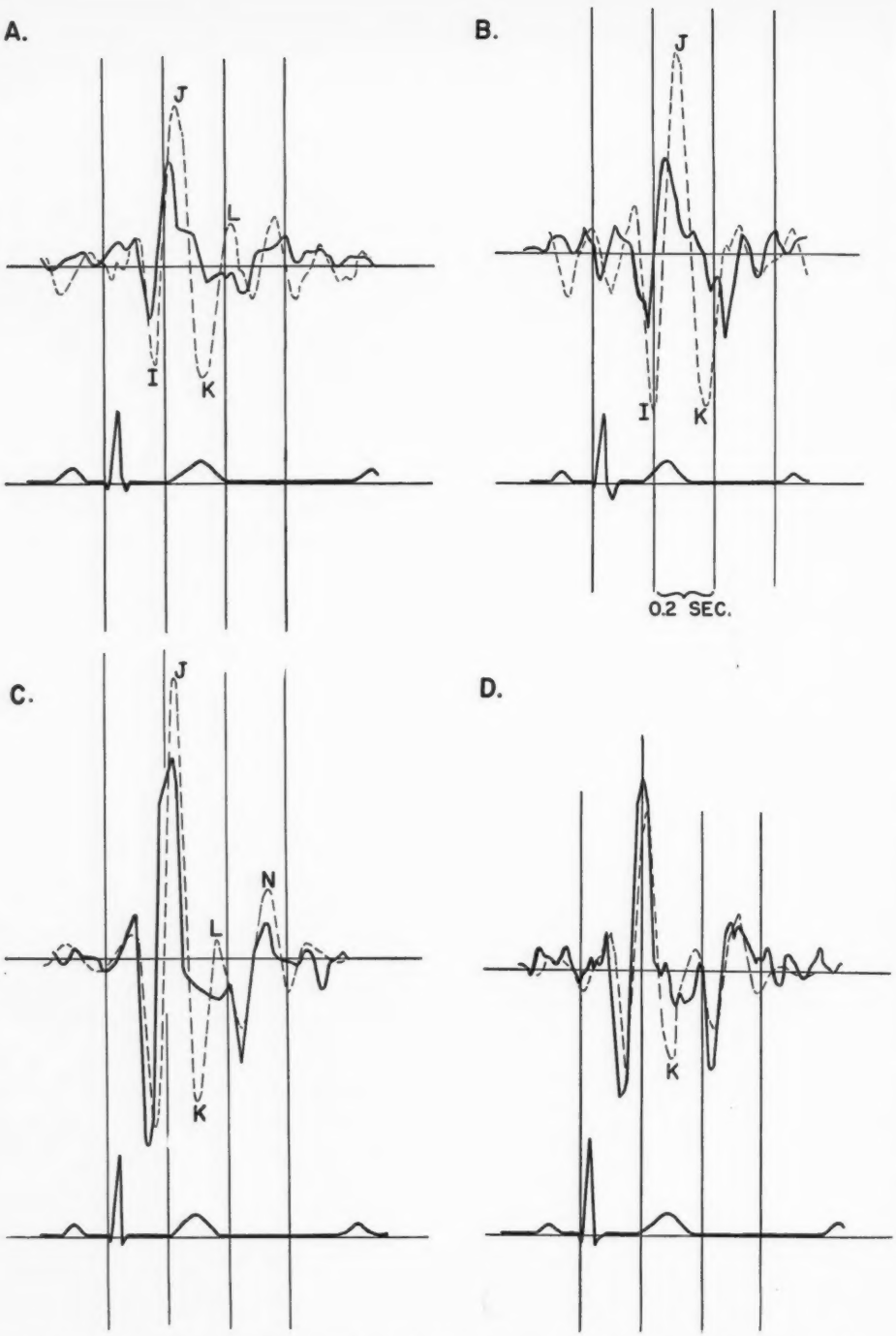


FIG. 3. Four examples of single complexes from normal records taken on the aperiodic and high-frequency beds, traced and superimposed to demonstrate their mutual relationship. The aperiodic bed records in this and all other similar figures in this paper are represented by the continuous line, the high-frequency bed records by the broken line; the lead II electrocardiogram is reproduced in each case to provide a reference for timing. For full discussion of this figure see the text.

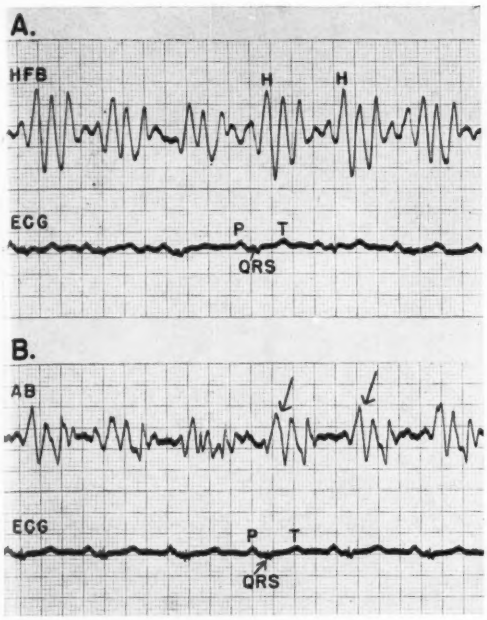


FIG. 4

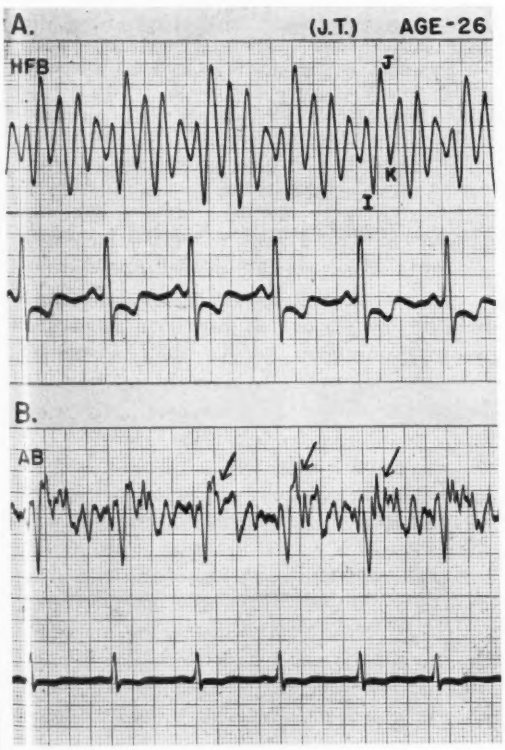


FIG. 6

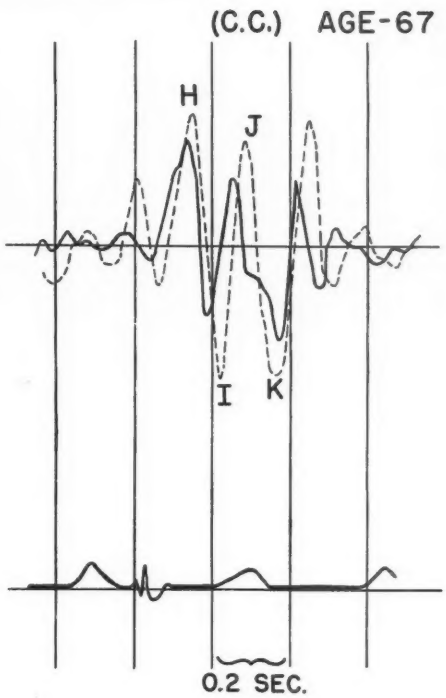


FIG. 5

FIG. 4. High-frequency bed (HFB, above) and aperiodic bed records (AB, below) together with the simultaneous lead II electrocardiogram in each case, as in all similar figures in this paper, from a 67 year old, clinically normal man. Both records are abnormal because of very large initial headward deflections (H waves); note the similarity of the abnormality in the two records. (See figure 5)

FIG. 5. Superimposed single complexes from the two records of the subject shown in figure 4, to demonstrate their relationship more clearly. (The aperiodic bed record is shown with a continuous line.)

FIG. 6. Ballistocardiograms (high-frequency bed above and aperiodic below) from J. T., a 26 year old man, with coarctation of the aorta and aortic regurgitation. The amplitude of the high-frequency bed record is large, probably related to the aortic incompetence, but the K wave is clearly shortened as compared with the I and M waves. Every complex of the aperiodic bed record contains a large, abnormal, long-acting headward deflection (marked with arrows) corresponding in time to the K wave of the other record. (See figure 7)

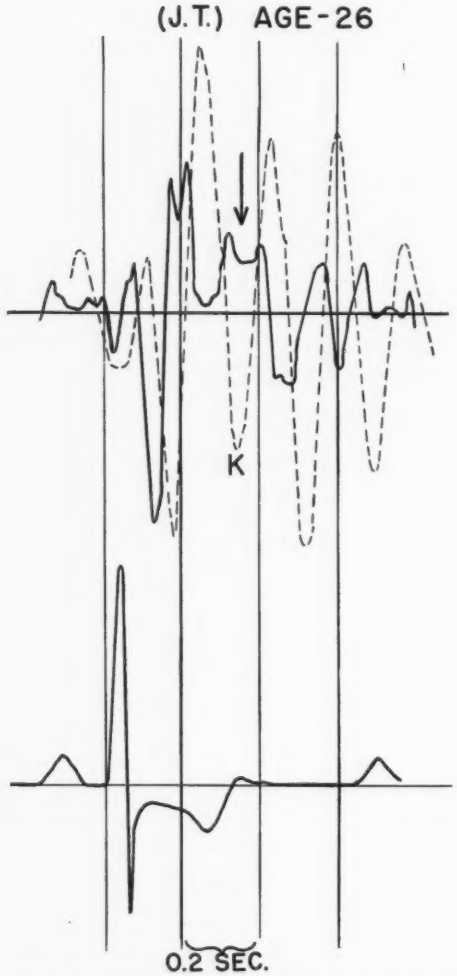


FIG. 7. Superimposed single complexes from the two records of the subject with coarctation of the aorta shown in figure 6. Note how the abnormal headward-acting force, shown by the deflection marked with the arrow, in the aperiodic bed record is so timed as to act against the K wave deflection in the high frequency bed record.

and to correct for any parallax error in relating them to the electrocardiogram. It can be seen that in the early part of the systolic complex the waves in the two records roughly correspond but that those from the high-frequency bed occur slightly later than those from the other. Thus the aperiodic ballistocardiogram contains waves which resemble the H, I and J

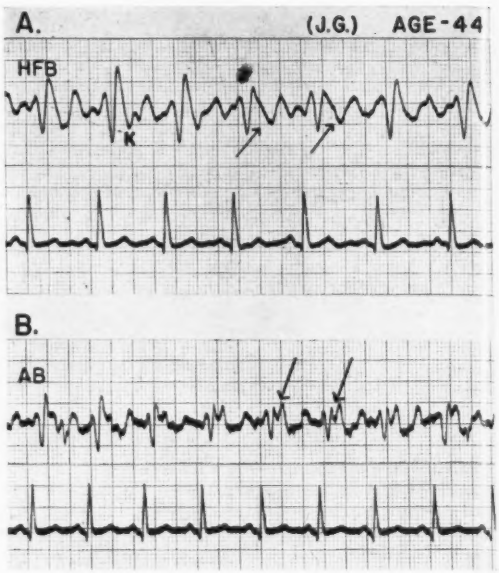


FIG. 8. The two records (high-frequency bed above, aperiodic below) from a 44 year old man with coronary artery disease. The high-frequency bed record shows shortening or absence of the K wave varying with respiration. In the aperiodic bed record there appears an abnormal, headward wave (marked by arrows) in each complex, corresponding in time to the K wave in the other record, which shows similar respiratory variation.

waves of the record from the high-frequency bed, and we may justifiably assume that the forces thus represented are those which give rise to the corresponding named waves in the record from the high-frequency bed. Inspection immediately reveals that there is, in the normal records, no wave in the aperiodic bed complex corresponding to the K wave. Starr originally believed that the K wave was largely an artefact due to after-oscillation,[3] and this observation would suggest that it is. The L wave also is not represented, but the last two waves in the aperiodic bed records correspond well to the M and N waves; this may be significant but could be fortuitous. Even if the M and N waves do not actually result from the forces occurring at the same time in the aperiodic bed record, the manner in which their amplitude differs from simple damped vibrations after the J wave can be explained on the basis

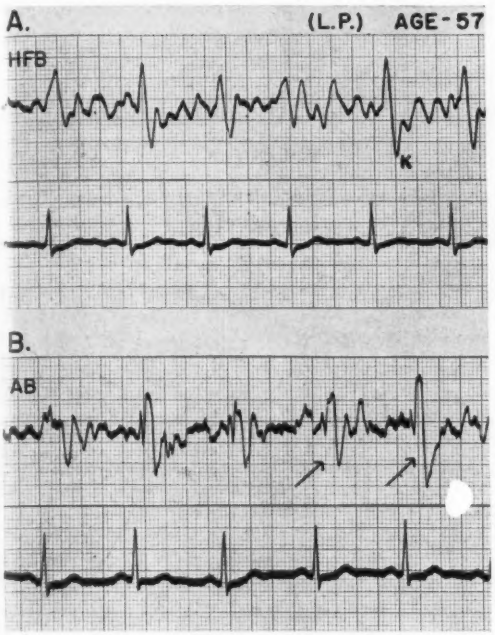


FIG. 9. The two records (high-frequency above, aperiodic below) from a man, 57 years old, with mild hypertensive cardiovascular disease (B.P. 175/100). The high-frequency bed record is variable, but in most complexes the I wave is short and the K deepened. The aperiodic bed record shows shortening of the initial footward deflection and the appearance of large abnormal footward waves (marked with arrows in two complexes) corresponding in time to the K wave. (See figure 10)

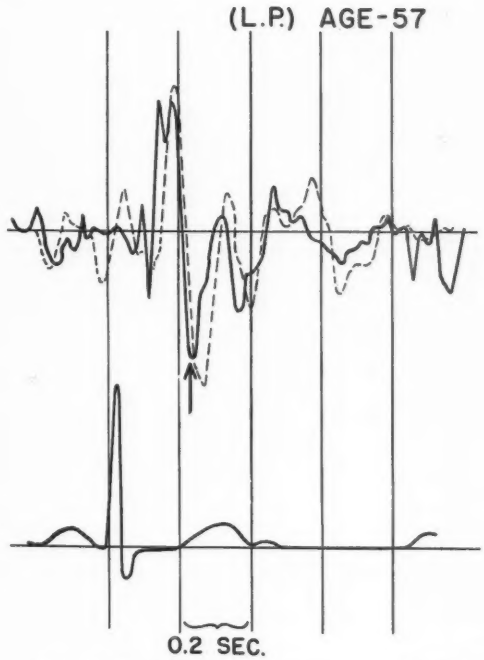


FIG. 10. Superimposed single complexes from the two records of the subject shown in figure 9. The close correspondence between the abnormal footward waves in the aperiodic bed complex and the deepened K wave in the other complex is well shown.

of impressed forces occurring at that time. Brown and his co-workers[12, 13] and others[14] have pointed out that the features just referred to indicate that new forces were acting there, for if these waves were due to simple underdamped after-oscillations alone they would fall equally astride the baseline with a decline in amplitude instead of, as is usually seen, the L wave being close to the baseline with the M and N being of larger amplitude below and above it. The portion of the record from the high-frequency bed following the J wave would thus seem to exemplify compounded effects of after-oscillation and freshly impressed forces.

The relation of the normal record from the high-frequency bed to the tracing from the aperiodic bed can thus be readily understood in terms of the analysis outlined above.

Abnormal Records

Further confirmation of this relationship has been sought and obtained in a variety of abnormal records. Thus we have found that patients with large H waves in the high-frequency record also have increased amplitude of the initial headward waves in the aperiodic ballistocardiogram. Figure 4 is from a clinically normal man, aged 67 years, and shows a quite abnormal record from the high-frequency bed with very large H waves dominating most of the complexes; the aperiodic bed record in this man shows similar very large initial headward waves. The timing of the waves in the remainder of the complexes is somewhat disturbed by this large deflection, as is often the case; in addition, there is an abnormal head-

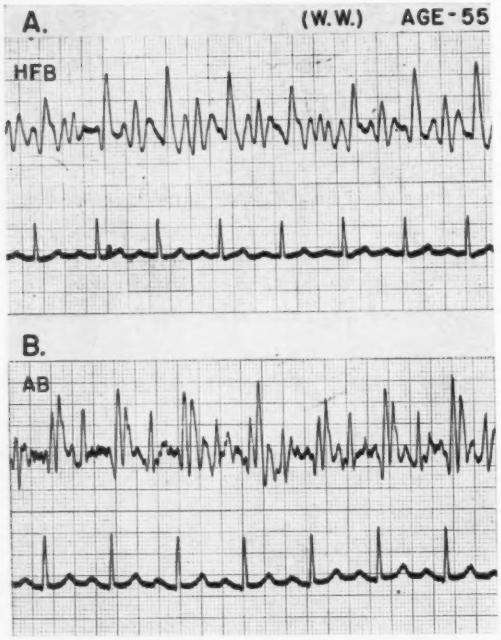


FIG. 11. The high-frequency bed (above) and aperiodic bed ballistocardiograms from a 55 year old man with syphilitic aortic incompetence and multiple aortic aneurysms. All the waves in the high-frequency bed record, as judged by their timing in relation to the lead II electrocardiogram, are abnormal. Note that the aperiodic bed record has a similar abnormal form except that here the largest systolic components are two large, fast headward waves occurring at about the same time as the single large wave in the high-frequency bed record. (See text)

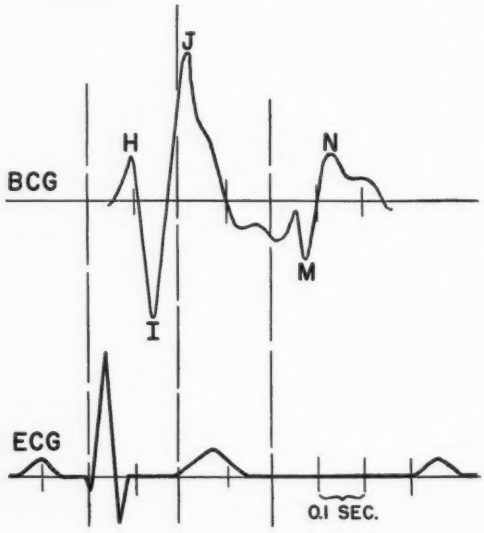


FIG. 12. A diagrammatic representation of an average normal complex of the aperiodic bed acceleration ballistocardiogram together with an electrocardiogram for timing. This shows the main deflections so far recognized as occurring uniformly in young normal subjects. The tentative nomenclature, referred to in the text, is indicated.

ward deflection in the record from the aperiodic bed occurring about 0.4 second after the Q wave in the lead II electrocardiogram which corresponds in the record from the high-frequency bed to a very large L wave, often exceeding the J in amplitude. These relations are more clearly seen in figure 5.

More interest attaches to changes in the K wave in the records from the high-frequency bed. As already mentioned, Starr[3] originally thought this wave was an artefact due to after-oscillation but Hamilton and his colleagues[15] postulated that it was produced by a footward acting force. This force was supposed to be generated when the normal, rapid footward flow of blood along the descending aorta was abruptly slowed by the peripheral resistance of the smaller vessels in the lower extremities. It is generally recognized that in coarctation of the aorta the K wave is shortened or even absent[16, 17]; this change has been explained[15, 18, 19] as resulting from the diminution, by the coarctation, of the normal blood flow in the descending aorta with consequent impairment of the mechanism producing the K wave. This observed change in coarctation could be regarded as supporting Hamilton's hypothesis, it being argued that if the K wave arose simply as an after-oscillation it ought always to follow a J wave of adequate amplitude, and that shortening as in coarctation must indicate reduction of some force which normally acts to produce it. This is not a valid argument, however, for a deflection normally occurring as an after-oscillation could be more or less canceled by a contrarily acting abnormal force.

In figure 6 are shown the two records from a young man (26 years) with coarctation of the

orta and some degree of aortic regurgitation; he over-all amplitude of the high-frequency ed complexes is large, probably due to the alvular incompetence, but the K wave is reatly shortened relative to the I and M aves. In the aperiodic bed record there is an bnormal, moderately large, headward-acting orce timed just so as to coincide with the K ave. This relationship is shown more clearly n figure 7. Another patient, a 44 year old man ith coronary artery disease, showed slurring of the J-K segment and shortening of the K, arying with respiration, in his high-frequency ed record (fig. 8). Again the aperiodic bed complexes show abnormal, headward forces, similarly varying with respiration, and so timed as to act against the K wave.

Another well-known abnormal form of the high-frequency bed complex involving the K wave is that called by Starr[20] the "late downstroke pattern" and commonly associated with hypertension. In this pattern the amplitude of the early part of the systolic complex is reduced while the K wave is unaltered or increased. We have not so far obtained a clear-cut example of this form change in this small series, but the records in figure 9 and 10 illustrate features suggesting the development of this abnormality in a man aged 57 years with mild hypertensive disease. The aperiodic ballistocardiogram in this patient shows a generally similar form with a large abnormal footward wave representing a new force occurring at such a time as would be expected to augment the K wave in the record from the high-frequency bed. This suggests that the K wave in the late downstroke pattern is at least largely due to an abnormal force.

Of considerable interest also were the records shown in figure 11 from a patient with syphilitic aortic incompetence and multiple aortic aneurysms. The complexes in the record from the high-frequency bed were composed entirely of abnormal waves as judged by their timing; the record from the aperiodic ballistocardiograph showed a very similar form with one major exception. In the latter record the largest systolic components are two large, fast, headward waves occurring between 0.10 and 0.20 second after the Q wave of the lead II electrocardiogram. The high-frequency record in this region shows only one large headward wave with a knee on its downstroke; we interpret this difference as an indication of the failure of the high-frequency bed to follow faithfully the faster phenomena shown in the other record.

Discussion

We have described and illustrated above various individual examples to show the relation between the two records in a variety of patterns. It should be emphasized that these records were selected as illustrations only and that the same type of relationship was found in all the other records we examined.

From this study we conclude that the relationship between the records from the high-frequency bed and the aperiodic bed is in keeping with our predictions based on an analysis of their respective behaviors. This finding provides observational support for the validity of this analysis. Records from aperiodic or closely related types of beds with similar mechanical behavior[6, 21, 22] can be regarded as representing more faithfully the motions of the body, considered as a unified mass, resulting from cardiovascular activity. Acceleration records will reflect the acceleration of the body and, hence, taking into account its mass, the force acting on it; displacement records will reflect displacement of the body and, hence, shifts in its center of gravity internally due to changes of the position of blood and the heart during each cardiac cycle (as described by Burger and co-workers[6]). Displacement records from the high-frequency bed, and also of the direct-body type, reflect predominantly the slower forces acting on the body but with the distortions described above.

The fact that both the aperiodic bed acceleration records and the displacement records from the high-frequency bed show to a greater or lesser extent the forces acting on the body as a result of cardiovascular activity has important implications. The close correspondence between many of the waves in the two records, demonstrated here, suggests that the corresponding waves in the aperiodic bed acceleration records represent more or less the same events which give rise to the H, I, J, M, and N waves of the

high-frequency bed displacement records. These letters, as applied to the appropriate waves in the records from the high-frequency bed, have now many years of generally accepted usage to their credit so that their retention would seem best suited to promote understanding of the newer type of records. For this reason these letters have been used to name the appropriate waves in the aperiodic bed records as shown in figure 12. The interval between the J and M waves may be referred to as the J-M segment and, in view of its variable form, suitable descriptive terms may be applied to it as seem necessary.*

Summary

On the basis of a theoretic and experimental analysis of its behavior it is believed that displacement records from the high-frequency bed ballistocardiograph reflect grossly, but subject to significant distortions, the forces impressed on the body by the cardiovascular "generator." A light platform floating on mercury has been used to obtain ballistocardiograms; this apparatus, because of its lack of restoring force, has been termed the "aperiodic ballistocardiograph." Acceleration records from this system are thought to represent more faithfully the forces acting on the body.

A relationship between the form of these two types of records has been predicted and confirmation of it sought in records obtained from 80 subjects. In both normal and abnormal records of varying types the expected relationship has been consistently observed; this finding provides factual support for our views on the behavior of these ballistocardiographic systems. It also provides a sounder basis for analyzing the wave form of records from Starr-type beds. The following generalizations regarding ballistocardiograms from these high-frequency instruments may be made:

1. The records reflect, in a general way, the forces acting on the human body, the slowest forces being the most faithfully represented.

2. Errors in phase, amplitude and frequency content are introduced because of the soft, elastic coupling between the body mass and its supporting surface and because of the weight and rigidity of the latter.

3. The H, I, J, M and N waves of normal records do, in fact, represent true forces applied to the body but are delayed in time. Since no forces corresponding to the normal K and L waves were consistently observed, it must be assumed that these represent the passive after-oscillations characteristic of underdamped, vibratory systems. However, unusually deep K waves may result from the addition of a new and abnormal footward force to the normal passive K wave afteroscillation. Conversely, short or absent K waves may be produced when an abnormal headward force occurs at such a time as to partially or completely cancel the normal K afterfling.

4. In general, our studies tend to support Starr's contention that ballistocardiograms from high-frequency bed systems are related to the forces produced by cardiovascular activity.

Summario in Interlingua

Un analyse previemente publicate del reactiones mechanic del systemas ballistocardiographic currentemente in uso permitteva le prediction de certe relationes inter registrationes ab le lecto typo Starr a alte frequentia e le registrationes que representa non-distorquite fortias applicate al corpore per le "generator" cardiovascular. Iste secunde gruppo esseva registrationes del acceleration de un platteforma typo "lecto aperiodic a mercurio." Nos ha investigate le relationes inter le formas de iste duo typos de registrationes in 80 subjectos. In varie typos de registrationes normal e anormal le predicite relationes inter le duo typos de ballistocardiogramma esseva observate. Nos conclude que registrationes ab le lecto a alte frequentia reflecte grossiermente le plus lente fortias applicate al corpore. Sed quanto a phase, amplitude, e frequentia iste registrationes es distorquite, in parte a causa

* The American Heart Association's Committee on Ballistocardiographic Nomenclature is currently studying the problem of terminology for direct-body velocity and acceleration records and for very low frequency or aperiodic bed acceleration records. It is felt that the foregoing comments regarding nomenclature may be made without prejudice to the Committee's deliberations.

del qualitates elastic del superficie dorsal del corpore e in parte a causa del peso e rigiditate del platteforma.

REFERENCES

1 Harrison, W. K., and Talbot, S. A.: Dynamical description of the ballistocardiograph. Federation Proc. **12:** 62, 1953.

2 Talbot, S. A., and Harrison, W. K.: Dynamical basis of current ballistocardiographs. In preparation.

3 Starr, I., Rawson, A. J., Schroeder, H. A., and Joseph, N. R.: Studies on the estimation of the cardiac output in man, and of abnormalities in cardiac function from the heart's recoil and blood's impacts; the ballistocardiogram. Am. J. Physiol. **127:** 1, 1939.

4 Talbot, S. A., Deuchar, D. C., Davis F. W., Jr., and Scarborough, W. R.: The aperiodic ballistocardiograph. Bull. Johns Hopkins Hosp. **94:** 27, 1954.

5 Nickerson, J. L., and Curtis, H. J.: The design of the ballistocardiograph. Am. J. Physiol. **142:** 1, 1944.

6 Burger, H. C., Noordergraaf, A., and Verhagen, A. M. W.: Physical basis of the low frequency ballistocardiograph. Am. Heart J. **46:** 71, 1953.

7 Arbeit, S. R., and Lindner, N.: A new full frequency range calibrated ballistocardiograph. Am. Heart J. **45:** 52, 1953.

8 Scarborough, W. R., Beser, J., Talbot, S. A., Mason, R. E., Singewald, M. L., and Baker, B. M., Jr.: A method for recording ballistocardiographic vectors. Bull. Johns Hopkins Hosp. **87:** 235, 1950.

9 —, Mason, R. E., Davis, F. W., Jr., Singewald, M. L., Baker, B. M., Jr., and Lore, S. A.: A ballistocardiographic and electrocardiographic study of 328 patients with coronary artery disease. Am. Heart J. **44:** 645, 1952.

10 —, Davis, F. W., Jr., Baker, B. M., Jr., Mason, R. E., Singewald, M. L., Lore, S. A., and Fox, L. M.: A ballistocardiographic study of 369 apparently normal persons. Am. Heart J. **45:** 161, 1953.

11 Davis, F. W., Jr., Scarborough, W. R., Mason, R. E., Singewald, M. L., and Baker, B. M., Jr.: The effects of exercise and smoking on the electrocardiogram and ballistocardiogram of normal subjects and patients with coronary artery disease. Am. Heart J. **46:** 529, 1953.

12 Brown, H. R., Jr., and de Lalla, V., Jr.: Ballistocardiogram, description and clinical use. Am. J. Med. **9:** 718, 1950.

13 —, Jr., de Lalla, V., Jr., Epstein, M. A., and Hoffman, M. J.: Clinical ballistocardiography. New York, Macmillan, 1952. P. 67.

14 Pierce, J. R., Christianson, L., and Walker, R. P.: Time relationships of ballistocardiographic movements. Am. Heart J. **46:** 329, 1953.

15 Hamilton, W. F., Dow, P., and Remington, J. W.: The relationship between the cardiac ejection curve and the ballistocardiographic forces. Am. J. Physiol. **144:** 557, 1945.

16 Brown, H. R., Jr., Hoffman, M. J., and de Lalla, V., Jr.: Ballistocardiogram in coarctation of the aorta. New England J. Med. **240:** 715, 1949.

17 Scarborough, W. R., Davis, F. W., Jr., Baker, B. M., Jr., Mason, R. E., and Singewald, M. L.: A review of ballistocardiography. Am. Heart J. **44:** 910, 1952.

18 Nickerson, J. L.: Some observations on the ballistocardiographic pattern with special reference to the H and K waves. J. Clin. Invest. **28:** 369, 1949.

19 Tannenbaum, O., Schack, J. A., and Vesell, H.: Relationship between ballistocardiographic forces and certain events in the cardiac cycle. Circulation **6:** 586, 1952.

20 Starr, I., and Schroeder, H. A.: Ballistocardiogram. II, Normal standards, abnormalities commonly found in diseases of the heart and circulation and their significance. J. Clin. Invest. **19:** 437, 1940.

21 von Wittern, W. W.: Ballistocardiography with elimination of the influence of the vibration properties of the body. Am. Heart J. **46:** 705, 1953.

22 Jonnart, L., and Ghys, A.: A study of the human ballistocardiogram. II. The acceleration ballistocardiogram. Acta cardiol. **8:** 232, 1953

The Effect of Ventricular Systole on Auricular Rhythm in Auriculoventricular Block

By MAURICIO B. ROSENBAUM, M.D. AND EUGENE LEPESCHKIN, M.D.

In some cases of complete A-V block the curve of the duration of P-P intervals showed a sudden dip with a gradual return, during or after the T wave. This positive chronotropic (accelerating) effect of ventricular systole is probably caused by the traction exerted on the right auricle by the contracting ventricle. Other cases showed a sudden rise in the curve of P-P intervals late in diastole, followed by a gradual return. This negative chronotropic (slowing) effect is probably caused by a vagal reflex precipitated by stimulation of the arterial pressoreceptors by the pulse wave. The interplay of these two effects determines whether the P-P intervals containing QRS will be shorter than those not containing it, or whether the relation is reversed (paradox effect).

IT HAS been frequently observed that in cases of auriculoventricular block the auricular P-P intervals which contain a ventricular QRS complex are shorter than those which do not contain it. According to previous papers[14, 15, 25, 32] which also contain reviews of the older literature, a pronounced shortening of these intervals was present in 42 per cent of 147 reported cases, while a slight or inconstant shortening or no change appeared in 54.5 per cent. In 3.5 per cent of the cases, the P-P intervals containing QRS complexes were found to be longer than those not containing it; we shall designate this behavior as "paradox" and the P-P intervals exhibiting it as "paradoxical". Many explanations have been proposed for the shortening of the P-P interval containing a QRS complex, but none of these appear completely satisfactory. The purpose of the present paper is to make a more detailed study than has been made heretofore in cases showing a definite relation between the duration of the P-P interval and the time of occurrence of the QRS complex, and to test the applicability of the various possible mechanisms in the light of our findings.

We have used five general methods of approach in our studies. In the first of these, we planned to make an exact analysis of the effect of the time of appearance of a given P-P interval after the QRS complex on the duration of this interval, in cases of complete A-V block. The second approach was to study the behavior of the P-P interval during the appearance or disappearance of 2:1 A-V block. The third group of observations concerned the behavior of this interval in cases where a slow idioventricular rhythm in complete A-V block is interrupted by premature ectopic ventricular beats. A fourth method was to study the effect of atropine or exercise on the behavior of P-P interval. The last group of observations concerned cases of auricular paroxysmal tachycardia with incomplete A-V block.

Only electrocardiograms in which the P waves were clearly visible were used for measurement. As the P waves are more or less rounded in shape and also often show slight variations in their configuration with respiration, the error of measurement in identifying the corresponding points of two successive P waves may reach 0.02 second. Because of this error, only electrocardiograms showing variations in the P-P intervals exceeding 0.03 second were used. If a P wave was partly superimposed on a QRS complex, only those parts of the P waves which were seen clearly were used for measurement of the P-P interval; these parts could be identified readily in most cases, as the P wave usually exceeds the QRS complex in duration.

1. Effect of Ventricular Systole on the P-P Interval in Complete A-V Block

As the purpose of this study was to obtain a curve expressing the influence of different

From the Division of Experimental Medicine, University of Vermont, College of Medicine, and the Bishop DeGoesbriand Hospital, Burlington, Vermont.

This investigation was aided by the Grant H-1486 of the National Heart Institute, National Institutes of Health, United States Public Health Service.

This work was done during the tenure of an Established Investigatorship of the American Heart Association by Dr. Lepeschkin.

phases of ventricular systole and diastole on the P-P interval, only cases in which the P waves appeared in widely differing relationships with the QRS complex could be used. Cases of complete A-V block proved best suited for this particular purpose. In order to obtain a statistically significant number of points for each phase of the ventricular cycle, it was necessary to select cases in which very long electrocardiographic tracings were taken. A case of this kind was reported in detail in the paper by Roth and Kisch[31], but a presentation of the results of their analysis in the form of a curve was not carried out in their original paper. In figure 1a, a total of 128 P-P intervals listed in table 4 of their paper is plotted against the time of appearance of the P wave concluding this interval with respect to the QRS complex. The continuous line in the graph is a smoothed curve based on average P-P values

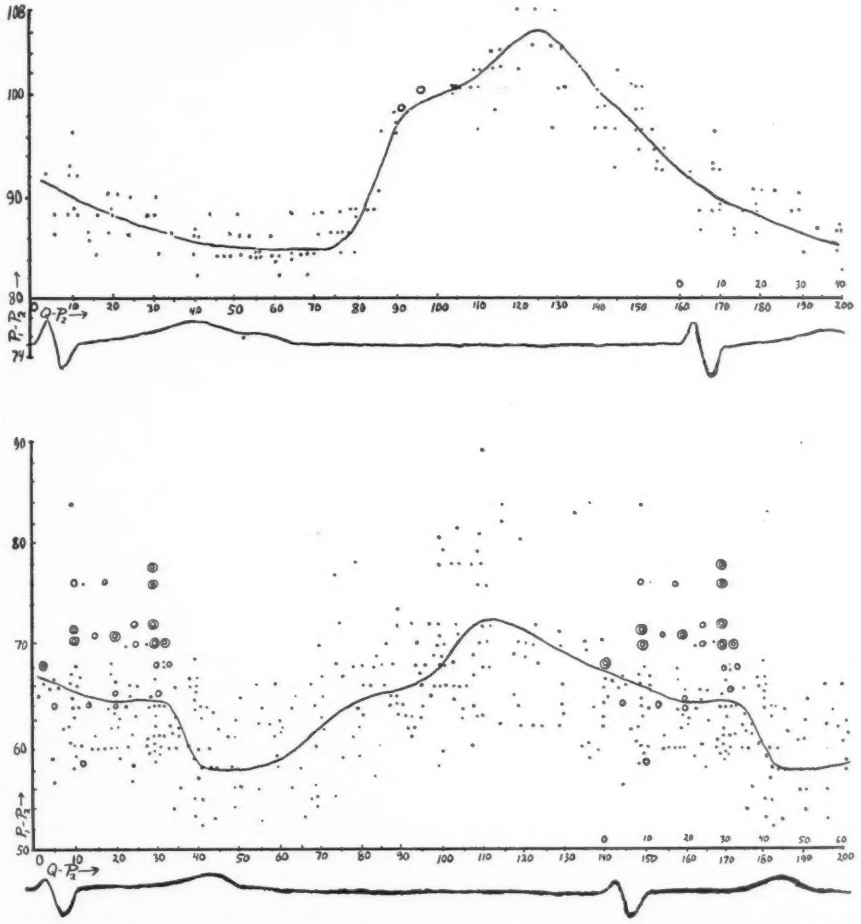


FIG. 1. Relation between the P-P interval (P_1-P_2) and the interval from the beginning of QRS to the beginning of the P wave concluding this interval (Q-P_2), in two cases of complete A-V block. The ventricular complexes are drawn to scale underneath each graph. Points indicated by circles correspond to P-P intervals showing a paradox relation to ventricular systole. Those indicated by single circles correspond to P-P intervals containing a QRS complex but exceeding the P-P interval which precedes or follows it. Points indicated by double circles correspond to P-P intervals containing a QRS complex and exceeding both the P-P interval which follows it and the one which precedes it. *a:* Case of table 4 of Roth and Kisch[31]. *b:* Case of table 2 of this paper.

within 0.1 second of each Q-P interval. It can be seen clearly that P waves falling later than about 0.8 second after the QRS complex tend to terminate P-P intervals which are considerably longer than those terminated by P waves falling earlier; this tendency is maximal for P waves appearing 1.2 second after the beginning of QRS. P waves appearing later are again less delayed. The entire curve of P-P intervals has a sharp ascent and gradual descent, resembling the arterial pulse wave in its contour. We shall designate this slowing effect of ventricular systole on auricular rhythm as a "negative chronotropic effect".

The two P-P intervals indicated by circles are paradoxical, that is, they are longer than intervals following or preceding them in spite of the fact that they contain a QRS complex. These intervals do not deviate from the general trend of the curve and are grouped around a Q-P value of 0.95 second. The P-Q interval of the preceding P wave (P-P minus Q-P) is about 0.05 second. The paradoxic behavior of the P-P intervals is evidently caused in this case by the fact that the influence which tends to prolong the P-P interval is sufficiently strong at this time.

Figure 1b represents an analysis of the P-P intervals of the case described in table 2 and illustrated in figure 3a of the present paper, carried out in a manner similar to that used in figure 1a. In this case, a total of 325 P-P intervals, registered on four different occasions, is plotted against the time of occurrence of the P wave concluding it in relation to the preceding QRS complex. Because of the fluctuations of the basic heart rate, the scatter of the P-P values for each Q-P interval is considerable. However, it is clear that there is a definite minimum at about 0.5 second after the beginning of QRS and a less pronounced maximum at about 1.1 second. In contradistinction to the curve of Figure 1a, the descent of the curve is steep while its ascent is gradual and seems to have a short plateau at about 0.85 second. We shall designate this accelerating effect of ventricular systole on auricular rhythm as a "positive chronotropic effect". The time of the beginning of this effect is difficult to determine because of the gradual slope of the curve, but it seems to be about 0.90 second.

Contrary to the case of figure 1a, the paradoxic P-P intervals of figure 1b are confined to the first 0.35 second of the Q-P interval, and the P-Q distances of the P wave initiating these intervals tend to be longer than average. The difference in the pattern of the paradoxic P-P intervals compared with that shown in Figure 1a can be explained by the fact that the P-P intervals in Figure 1b are shorter than those in 1a, and in the former the positive chronotropic effect seems to predominate over the negative one. As a consequence, P waves occurring within 0.35 second of the QRS complex are not affected in their time of appearance, and the corresponding P-P intervals are long even though they contain a QRS complex.

The graphic analysis described in the preceding paragraphs was applied to eight additional cases published in the literature; two of these[2, 23] were already presented in graphic form. The results are summarized in table 3, which also includes the two cases described in detail above. The cases are arranged in the order of increasing ventricular rates. It can be seen that of the 10 cases included in this table, six exhibited a behavior similar to that shown in figure 1a in that they showed an abrupt rise of the P-P intervals with increasing Q-P intervals, followed by a gradual fall. In these cases, therefore, only a negative chronotropic effect on the auricular rhythm seemed to be present. This effect began at Q-P intervals of 0.50 to 1.70 second and reached a maximum at 1.10 to 2.10 second.

One of the 10 cases of table 3 (case 9) showed a sudden decrease of the P-P intervals with a gradual return to the base line; the maximum of this decrease occurred at 0.35 second after beginning of QRS. A second sharp decrease took place at 0.65 second, while the increase of P-P which followed was gradual. This case was considered as showing no negative chronotropic effect of ventricular systole, but only a positive chronotropic effect with two maxima. The duration of the "dip" in the P-P curve corresponding to the second maximum was only 0.20 second and the number of observations on which it was based was small; nevertheless, as it was almost identical in form and location with the dips of case 4, which were clearly seen on two different occasions, it seems unlikely

that it should be a spurious effect due to a chance distribution. In 3 of the 10 cases (cases 4, 8 and 10), finally, both a sudden rise and a sudden dip in the curve of P-P values appeared to be present, so that both a positive and a negative chronotropic effect was assumed in these cases. The maxima of the positive chronotropic effect ranged from 0.35 to 0.85 second, while the earliest time of appearance of this effect was 0.15 to 0.75 second after the beginning of QRS.

2. The P-P Interval in Cases of Transient A-V Block

In table 1, the P-P intervals during the spontaneous appearance and disappearance of 2:1 A-V block in another patient are recorded.

Table 1.—*Consecutive P-P Intervals During the Appearance (A) and Disappearance (B) of 2:1 A-V Block (numbers provided with asterisks correspond to P-P intervals not containing a QRS complex)*

ECG	Group	P-P Intervals in 0.01 Seconds
1	B	63–72*–65–68
2	A	68–68–73*–66
3	A	70–70–74*–66
4	AA	70–70–75*–69–69–69*–65–68*–63–63*–62–65*
5	BA	67–73*–66–69–68–76*–66–70–71
6	B	63–71*–63–71*–63–71*–63–71–71–71
7	A	69–69–81*–69–72–77
8	A	70–70–69–68–71*–63–73*–61
9	B	64–75*–64–77*–65–78*–69–71–71–73–79–82–80–77–77–77
10	A	69–70–71*–66–72*–65–69*–64–73*
11	B	64–69*–64–70*–64–71*–68–76–78–78–78
12	B	57–61*–56–67*–59–67*–61–73*–64–71–71–76–79–82
13	B	52–57*–52–54*–52–58*–53–75*–65–74–82–72–72
14	B	77*–70–73–70–74–74–74
15	AA	73–73–73–80*–70–71–74*–66–72*
16	B	64–76*–64–76*–66–72–74–73–75
17	A	72–72–75–72–70–73*–69
18	A	66–69–74*–71–94–87–81
19	B	70*–61–70*–63–73*–63–73*–65–73

The patient referred to in this table (C. M.) was a 53 year old woman with hypertensive heart disease, slight left ventricular enlargement but no heart failure. The blood pressure ranged from 190/100 to 270/130. During transition from 1:1 to 2:1 conduction small changes in the duration of the P-R interval (Wenckebach phenomenon) occurred.

These are taken from five electrocardiograms registered at rest during a 10-month period. There were 12 instances in which 2:1 A-V block appeared (group A); these are illustrated by the middle of figure 2a and by figure 2b. In this case, the first P-P interval which does not contain a QRS complex (P-P*) and the succeeding P-P interval which contains this complex (P-P) were expressed as a percentage of the last P-P interval during 1:1 conduction. The calculations showed that the P-P* was on the average 6.69 per cent longer than the last P-P interval, the individual variations being from 0 per cent (in ECG 4 of table 1) to 17 per cent. The reason there was no increase in ECG 4 is that this electrocardiogram showed a definite tendency of the P-P intervals to decrease throughout the tracing. The first P-P interval with QRS, following the missed A-V conduction, showed an average shortening of 4.03 per cent compared with the last P-P interval preceding the block. The individual variations ranged from an increase of 2.9 per cent (in ECG 18 of table 1) to a decrease of 8.5 per cent. The increase in ECG 18 of the P-P interval and the absence of change in ECG 7 can be explained by the tendency of P-P to increase towards the end of the tracing. The conclusions which we may draw from this series is that the absence of ventricular systole during one P-P interval causes a definite prolongation of this interval and a slight shortening of the following P-P interval.

There were 10 instances in which a 2:1 A-V block disappeared (group B). These are illustrated at the beginning and end of figure 1a. In this series, the first and second P-P intervals with normal conduction were expressed as a percentage of the last P-P interval not containing a QRS complex. The first P-P interval showed an average decrease of 10.48 per cent, the range being from 4.2 to 13.3 per cent. The second P-P interval showed an average decrease of 2.72 per cent, the individual variations ranging from an increase of 7 per cent (in ECG 11 of table 1) to a decrease of 8.9 per cent. The increase in the second P-R in ECG 11 and the absence of any change in ECG 7 and 19 of table 1 is due to a trend of the P-P intervals to increase through the tracings. The results of

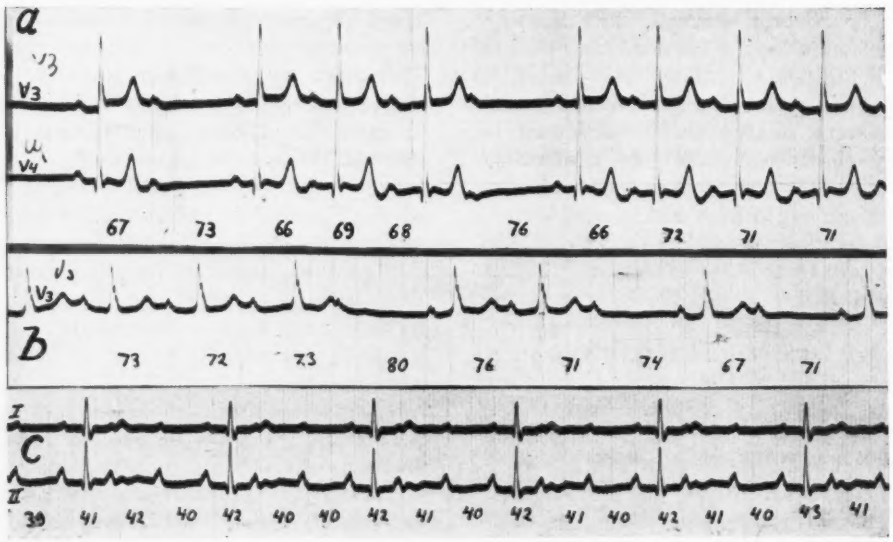


FIG. 2. Transient 2:1 A-V block (case of table 1). The consecutive P-P intervals (in 0.01 second) are indicated at the lower edge of each tracing. *a:* ECG 5 of table 1. *b:* ECG 15 of table 1. *c:* One minute after exercise.

this series thus indicate that not only the first but also the second P-P interval after restitution of normal A-V conduction is shorter than the P-P interval not containing a QRS complex.

Exceptions to the general trend described in the two preceding paragraphs were caused by spontaneous variations of the sinus rate, but even these variations were not sufficient to cause a paradoxic relation between the P-P intervals containing a QRS complex and the adjoining intervals not containing it; the former were always shorter than the latter.

3. Effect of Ventricular Ectopic Beats in Complete A-V Block on the P-P Interval

Table 2 represents the P-P intervals during the appearance and disappearance of ventricular ectopic beats in the case of complete A-V block depicted in figure 1b. In this case the appearance of an ectopic beat between two idioventricular beats would cause a hemodynamic situation resembling the reappearance of 1:1 conduction (fig. 3b), and accordingly the situation of group B in cases of 2:1 block. In seven instances of such a transition, the first P-P interval containing a QRS complex was on the average 6.91 per cent (2.7 to 10.1 per cent) shorter, while the second P-P interval with a QRS complex was 5.87 per cent (1.4 to 9.8 per cent) shorter, than the preceding P-P interval without QRS. As in the corresponding group B of patients with transient 2:1 block, the decrease of the second P-P interval is smaller than that of the first, but the difference is not as pronounced. A similar observation was made previously by Rasario.[29]

When the ectopic beats disappear and idioventricular rhythm is reestablished, the situation resembles that found at the time of appearance of 2:1 A-V block (group A). In this case the first P-P interval not containing a QRS group showed an average prolongation of 11.08 per cent (1.3 to 33.7 per cent) when compared with the last interval containing QRS, while the first P-P interval with QRS, appearing after the interval without QRS, showed an average decrease of 0.86 per cent when compared with the same interval. The individual values in this last case ranged from a decrease of 8.1 to an increase of 9.4 per cent. This means that disappearance of prematu e

TABLE 2.—*Consecutive P-P Intervals in a Case of Complete A-V Block During the Appearance (Group B) and Disappearance (Group A) of Ventricular Extrasystoles*

Numbers with asterisks correspond to P-P intervals not containing a QRS complex; numbers followed by "e" are intervals containing an extrasystole, while numbers followed by "i" are intervals containing the QRS complexes of the idioventricular rhythm)

EC.	Group	P-P Intervals in 0.01 Seconds
1	B	74*–68i–68e–66e–74*–73i–68e–74*–67i–63*
2	B	74*–63i–70*–65i–65e–69e–72*
3	AB	75*–68i–70e–97*–66i–78*–69i–72*
4	AB	69*–62i–68e–73*–71i–69e–72*
5	AB	70*–65i–72*–69i–70e–70e–75*–68i
6	AB	66i–67e–71*–66i–64e–72*
7	A	74e–75*–69i–68e–66e
8	A	75*–69i–68e–66e–77*–74i

The patient (P. R.) referred to in this table was a 38 year old woman, with chronic myocarditis due to Chagas' disease and variable hypertension, without heart failure. The blood pressure ranged from 155/80 to 205/100.

beats caused an increase of P-P comparable to that observed during appearance of 2:1 block, but that the first P-P interval with QRS after an interval without QRS was only insignificantly shorter than the last P-P interval of a series containing QRS complexes.

In a case of 3:1 A-V block with nodal escape beats, illustrated by Parsonnet and his coworkers[26], the P-P interval not containing QRS was on the average 9 per cent longer than the preceding interval with QRS, while the following interval with QRS was 3.1 per cent longer than this interval (group A). On the other hand, the first P-P interval with QRS after the interval without QRS was on the average 5.2 per cent shorter, while the second interval was 6.6 per cent shorter, than this interval (group B).

4. The Effect of Atropine and of Exercise

In the case whose details are shown in table 2, 1 mg. of atropine sulfate was injected intravenously, and the relation of the P-P intervals to the time of appearance of the P wave concluding them was plotted as in figure 1b. Immediately before atropine, the average P-P interval was 0.56 second and the maximum of the dip in the curve of P-P intervals appeared at about 0.45 second after QRS. The maximum of the rise seemed to be at about 0.95 second. At the beginning of the first minute after injection, the P-P intervals had an average of 0.47 second and showed a dip with a maximum at about 0.55 second (slightly delayed as compared with the value before atropine), while the maximum of the rise remained at about 0.95 second. At the end of the first minute and during the second and third minutes after injection, the average P-P interval was 0.38 second; the dip in the curve of P-P intervals was less pronounced and seemed to have a maximum at about 0.55 second; because of the increase in ventricular rate, no Q-P values at which a late rise of P-P would be expected were registered. Five and six minutes after the injection, coupled ventricular premature beats which were present singly on previous occasions (fig. 3b), now appeared continuously in the form of bigeminal rhythm (fig. 3c). At this time the P waves showed a peculiar group formation which was present in almost identical form during all of the 11 bigeminus groups which were registered. The P wave which appeared 0.25 to 0.30 second after the idioventricular QRS complex always terminated a P-P interval of 0.38 to 0.39 second. The next P wave, which occurred 0.07 to 0.12 second after the beginning of the premature beat and 0.67 to 0.72 second after the idioventricular beat, terminated a P-P interval of 0.41 to 0.42 second. The following P wave occurred 0.45 to 0.52 second after the extrasystole and terminated a P-P interval of 0.39 to 0.40 second. The following P wave, which occurred 0.85 to 0.90 second after the extrasystole, terminated a P-P interval of 0.37 to 0.38 second, and the last P wave occurred 1.25 to 1.30 second after the extrasystole and concluded a P-P interval of 0.40 to 0.41 second. If these groups of values were connected by a curve, this seemed to show a dip at about 0.45, a rise at 0.70, another dip at about 0.85, and a gradual rise up to 1.30 second. The three bigeminal groups registered 10 minutes after the injection show greater variability in the Q-P and P-P intervals, but these are situated on or around the P-P curve at 5 to 6 minutes.

When in the case shown in table 2 at rest the P-P interval containing a QRS complex was

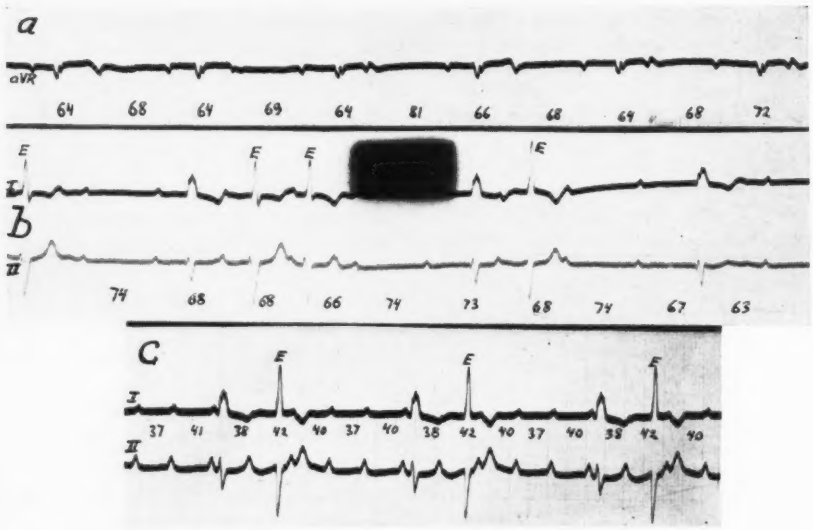


FIG. 3. Complete A-V block (case of table 2). The P-P intervals (in 0.01 second) are indicated at the lower edge of the tracing. Ventricular extrasystoles are indicated by the letter "E". *a:* Regular idioventricular rhythm (part of fig. 1b). The last P-P interval containing a QRS complex shows a paradoxic prolongation. *b:* Idioventricular rhythm, interrupted by ectopic beats (ECG 1 of table 2). *c:* Five to six minutes after 1 mg. atropine sulfate intravenously.

expressed as a percentage of the preceding P-P interval, which does not contain QRS, the former was found shorter in 85 per cent of the cases and longer in 15 per cent. The average shortening was about 7 while the average prolongation was only 3 per cent. It was already mentioned that a prolongation of the P-P interval containing QRS, which we designated as a "paradoxic behavior", appeared only when the second P wave of the P-P interval fell less than 0.35 second after the QRS complex. During the first minute after the injection of atropine, the shortening of the P-P interval containing QRS became progressively smaller as the P-P intervals decreased, and when they reached a value of 0.39 to 0.41 second, a shortening was observed with about the same frequency as a prolongation. During the second minute after atropine, the P-P intervals fell to 0.34 to 0.38 second, and all P-P intervals containing QRS complexes showed a paradoxic prolongation of, on the average, 5 per cent. Three minutes after atropine the durations of the P-P intervals were beginning to rise, and the intervals containing QRS complexes show little difference from those not containing it. Five to 10 minutes after atropine the P-P intervals again reach 0.37 to 0.42 second, and are again shorter if they contain a QRS complex. We have seen, therefore, that atropine caused a disappearance or reversal of the usual effect of QRS on the P-P interval containing it while the dip in the curve expressing the relation of P-P to Q-P was still present at an approximately normal time; the decrease of P-P during this dip was also of normal magnitude, when expressed as a percentage of the average P-P interval (7 per cent before and after atropine). The P waves terminating the paradoxical P-P intervals appeared always earlier than 0.35 second after QRS, as was the case without atropine. The cause of the paradoxic effect of QRS on P-P in this case was, therefore, the shortening of the P-P intervals, which caused the second P wave following QRS to appear during the dip of the P-P curve, instead of during the late rise, as was the case without atropine.

Many authors have remarked previously that the difference between P-P intervals containing QRS complexes and those not containing it becomes smaller or disappears completely after atropine.[9,

TABLE 3.—*Intervals (in 0.01 Second) from the Beginning of QRS to the Negative or Positive Chronotropic Effects of Ventricular Systole on the P Waves*

No.	Ref.	Case	Age	Sex	Diagnosis	Average R-R	Average P-P	Positive Chronotropic Effect			Negative Chronotropic Effect		
								Beginning	Maximum	Change of P-P	Beginning	Maximum	Change of P-P
1	17	1	67	M	Syphilis	270	90	—	—	—	170	210	+13%
2	23	1	48	M	?	200	85	—	—	—	95	120	+14%
3	2	1	?	?	?	176	73	—	—	—	50	115	+14%
4	10	Tables 1 and 2	52	F	Moderate hypertension	175	85	75	85	−13%	120	150	+11%
						150	75	70	85	−19%	120	140	+4%
5	31	Table 2	55	M	Arteriosclerosis. heart disease	160	70	—	—	—	64	111	+21%
6	31	Table 4	?	?	?	160	94	—	—	—	85	125	+17%
7	31	Table 5B	21	M	?	150	90	—	—	—	75	118	+17%
8	This paper	Table 2	38	F	Chagasic myocarditis, moderate hypert.	140	68	35	45	−13%	90?	110	+9%
9	10	Table 3	65	F	Moderate hypertension	135	70	15	35	−14%	—	—	—
								62?	65?	−12%?			
10	8	2	78	M	Arteriosclerosis	130	87	15	35	−11%	85	100	+2%

[14, 15, 31, 32]. This disappearance can be caused either by a complete disappearance of all effects of ventricular systole on the P-P intervals, or it can be merely an apparent disappearance, caused by a change in the time of appearance of the P waves in relation to the QRS complexes. The first type was present in the case of Matsuda and Tomono[23], where the P-P intervals were identical at all Q-P intervals of the P waves terminating them. This case showed only a negative chronotropic effect but no positive chronotropic effect of ventricular systole (case 2 of table 3). The second type was present in our case discussed in table 2 (case 8 of table 3), and also in the case illustrated by Corsi,[19] (case 4 of table 3). In this latter case, atropine caused a complete A-V block to be transformed into 2:1 block in which the P waves appeared only at those intervals after QRS which were situated between a rise and a dip in the P-P curve without atropine. In this case the disappearance of the difference between the P-P intervals could have been only an apparent one. Both of the cases showed a definite positive chronotropic effect of ventricular systole.

The effects of exercise were studied in the case described in table 1. Before exercise, 2:1 A-V block was present, and P waves occurring, on the average, 0.35 second after QRS complexes terminated P-P intervals with QRS, averaging 0.56 second, while P waves appearing around one second after QRS terminated P-P intervals without QRS, averaging 0.62 second. Immediately after exercise, complete A-V dissociation with an idioventricular rhythm was present, and P waves appearing 0.08 to 0.25 second after QRS terminated P-P intervals averaging 0.385 second; P waves appearing 0.30 to 0.90 second after QRS terminated P-P intervals averaging 0.37 second, while P waves appearing 0.92 to 1.22 second after QRS terminated P-P intervals having an average of 0.38 second. At this time the P-P intervals containing QRS accordingly showed a tendency to be longer than those not containing it. One minute after exercise, 3:1 A-V block appeared (fig. 2c), and P waves occurring around 0.20 second after QRS complexes terminated P-P intervals averaging 0.425 second, P waves falling around 0.60 second after QRS terminated P-P intervals averaging 0.410 second, while P waves appearing around 1 second after QRS complexes terminated P-P intervals averaging 0.4 second. At this time all P-P intervals containing QRS complexes were longer than those not containing it (paradoxic effect). About two minutes after exercise, 2:1 A-V block reappeared; at this time P waves appearing around 0.25 second after QRS as well as those appearing 0.75 second after QRS terminated P-P intervals of 0.48 second; the difference between P-P intervals containing QRS and those not containing it had disappeared. Three minutes after exercise the appearance of ventricular extrasystoles made the measurement of P-P intervals difficult. When uninterrupted 2:1

block reappeared, the P waves and P-P intervals had the same relation to the QRS complexes as before exercise.

The gradual transition between a paradoxic and the usual effect of the ventricular QRS complex on the P-P interval containing it, observed in the case described above during recovery from exercise, can be explained as follows. During the first minute after exercise the presence of a positive chronotropic effect of ventricular systole (about 5 per cent) from 0.25 to 1 second after QRS and a complete absence of a negative chronotropic effect can be assumed. The first P wave after QRS appears before the positive chronotropic effect has had time to manifest itself, and this leads to a paradoxic prolongation of the P-P interval which it concludes. Two minutes after exercise, the first P wave after QRS still appears before the positive chronotropic effect has set in, but the second P wave is now influenced by both the positive effect and by the negative chronotropic effect which has not begun to develop; this causes the P-P intervals of both P waves to become approximately equal. From the end of the third minute on, the first P wave after QRS appears late enough to be influenced by the positive chronotropic effect while the second P wave is influenced by the late negative chronotropic effect which is now fully developed. This leads to the usual shortening of the P-P interval containing QRS compared with the other intervals.

5. Paroxysmal Auricular Tachycardia With 2:1 A-V Block

We have seen occasional cases of auricular paroxysmal tachycardia with 2:1 A-V block which showed the same alternation of P-P intervals as cases of A-V block in normal sinus

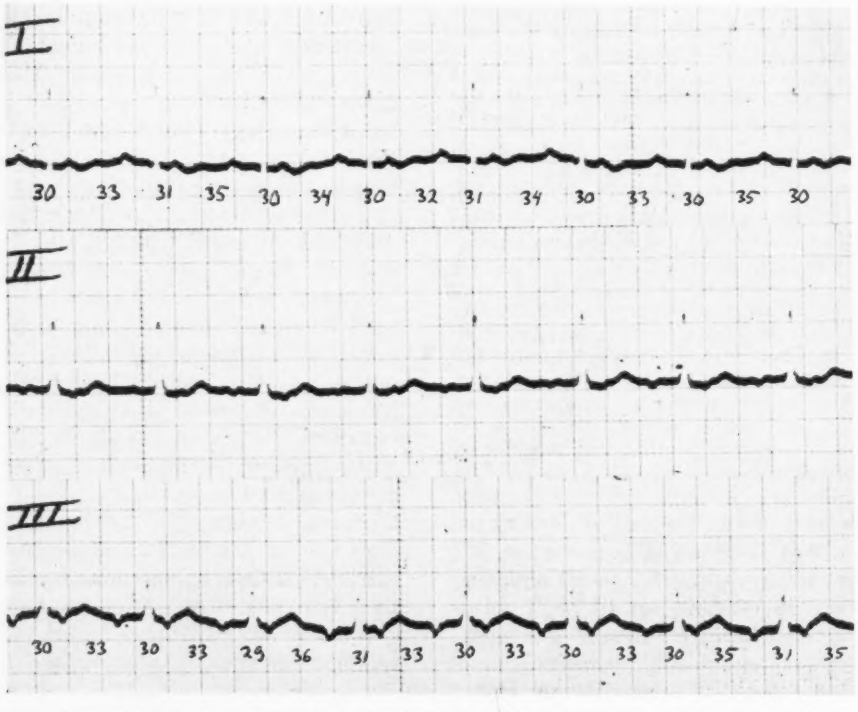


Fig. 4. Auricular tachycardia with 2:1 A-V block, in which the P-P intervals containing QRS are shorter than those not containing this complex. The P-P intervals are indicated on the electrocardiogram in 0.01 second. Fifty-six year old male with hypertensive heart disease and probable myocardial infarction. Courtesy of Seymour B. London, M.D., Miami Beach, Florida.

rhythm. One of these cases is illustrated in figure 4. In this case, the P waves appearing 0.2 to 0.13 second after QRS conclude P-P intervals of 0.29 to 0.31 second while P waves appearing 0.42 to 0.46 second after QRS conclude P-P intervals of 0.32 to 0.36 second. Docherd and co-workers[11] mention the occurrence of alternation of P-P intervals in their paper on paroxysmal auricular tachycardia with A-V block. We have measured the P-P intervals in the 40 cases illustrated in this paper. These intervals could be measured accurately in only 25 cases; of these, five cases showed variations of P-P intervals unrelated to the time of appearance of ventricular systole. Of the remaining 20 cases, P-P intervals containing a QRS complex were shorter than those not containing it in 11 cases, while in nine cases all P-P intervals were equal. A paradoxical behavior of the P-P intervals was never observed. In the cases showing the changes in P-P, the average value for P-P was 0.344 second, while this average was 0.332 second in the cases which did not show it. In the former, the P waves terminating the short P-P intervals appeared 0.06 to 0.21 second after the beginning of QRS, while those terminating the long P-P intervals appeared 0.31 to 0.54 second after QRS. In the cases with constant P-P intervals, these showed the same range in the time of appearance of the P waves terminating them. A similar effect of ventricular systole on auricular rhythm was present also in figures 8B, 9B and 20 of a paper by Barker and associates.[4] In the paper by Lown and co-authors,[22] their figure 1B shows a case of paroxysmal auricular tachycardia with variable 2:1 and 3:1 A-V block. In this case, P-P intervals containing QRS and concluded by P waves 0.12 second after QRS have an average duration of 0.31 second while the following P-P intervals without QRS, with P waves falling 0.45 second after QRS, have an average duration of 0.34 second. P-P intervals concluded by P waves occurring 0.77 second after QRS have again a short duration of 0.31 second.

Alternation in the auricular cycle length has been described also in cases of auricular tachycardia without A-V block,[5] and the objection could be made that the variations of P-P in the cases described in this section could have been caused by the same mechanism, and not by the alternate absence of ventricular systole. However, the short P-P intervals invariably contained a QRS complex while the long intervals did not. In Figure 2 of the paper of Barker and co-workers,[4] alternation of P-P intervals was present only during 2:1 A-V block and not during normal conduction; it is of interest that the P-P intervals in the latter case corresponded to the shorter P-P intervals in the presence of block. Furthermore, in Figure 1B of the paper of Lown and colleagues[22] the alternation disappeared as soon as the 2:1 block changed into 3:1 block, while the shortening of the P-P intervals containing QRS persisted. These observations definitely prove the dependence of the auricular arrhythmia on ventricular systole in these cases.

The fact that ventricular systole influences the P-P interval also in auricular tachycardia with A-V block is important because it demonstrates that the same mechanism is valid for ectopic auricular rhythms as for the normal sinus rhythm. On the other hand, the presence of the auricular arrhythmia at the high auricular rates occurring during this tachycardia is contrasted with its absence or reversal when similar sinus tachycardias are produced in A-V block by atropine or exercise.

Discussion

The observations reported in this paper indicate clearly that in most cases of A-V block where ventricular systole exerts an effect on the auricular rhythm, two mechanisms are responsible for this effect. One of these consists of a prolongation of the P-P intervals (negative chronotropic effect), while the other results in a shortening of these intervals (positive chronotropic effect). In the following paragraphs we shall discuss the possible physiological mechanisms responsible for each of these effects, and shall try to determine which of these is supported best by our observations and by the results of other physiological studies.

A. The Negative Chronotropic Effect of Ventricular Systole

1. Stimulation of the Arterial Vagal Pressoreceptors by the Pulse Wave

Wilson and Robinson[41] were the first to apply to a clinical case of A-V block the hypothesis of Erlanger and Blackman that the rise

of arterial pressure elicited by ventricular systole results in stimulation of the arterial pressoreceptors, which in turn causes a reflex vagal slowing and a delay of the second P wave following a ventricular QRS complex. This explanation was favored over all the others in most of the subsequent publications, it being usually considered as the only mechanism responsible for the auricular arrhythmia.[2, 13, 14, 15, 17, 23, 25, 31, 32, 33] As the arterial pulse wave begins suddenly and ends gradually, we would expect the curve representing the P-P intervals in their relation to the ventricular QRS complexes to have a sharp rise and a gradual descent if the auricular arrhythmia is caused by the pulse wave. We have seen in section I of this paper that this is actually the case in most cases of complete A-V block (table 3). A sudden negative chronotropic effect on P-P was the only mechanism responsible for the auricular arrhythmia in 6 of the 10 cases studied, and it seemed to be absent in only one of these. This was the case with the fastest ventricular and auricular rates, which accordingly may have shown a certain degree of vagal inhibition.

It can be seen in table 3 that the intervals from the beginning of QRS to the P waves terminating the longest P-P intervals ranged from one to 2.10 second; the earliest time at which the negative chronotropic effect appeared ranged from 0.50 to 1.70 second.

The period of latency of the maximum negative chronotropic vagal effect of ventricular systole on P-P consists of several components. The first of these, the period from the beginning of the QRS complex to the beginning of ventricular ejection, amounts to approximately 0.1 second and is practically constant. The second component, the conduction time of the pulse wave from the heart to the arterial pressoreceptor areas is about 0.05 second; it decreases with increasing age and blood pressure. The third component is the time necessary for the maximal pressure to be attained in the arterial system. This interval amounts to 0.15 to 0.30 second, parallels the duration of ventricular systole and therefore decreases with an increase of the heart rate; in the case of the carotid sinus, the point of maximum arterial pressure coincides approximately with the apex of the T wave of the electrocardiogram. The fourth component is the latency of the pressoreceptors, the fifth is the conduction time to the medulla, the sixth is the ganglionic transmission time in the vagal nucleus, the seventh is the conduction time in the vagal nerve to the cardiac ganglia, the eighth is the transmission time in these ganglia, and the ninth is the time necessary for a sufficient amount of acetylcholine to be liberated near the pacemaker of the sinus node and to diffuse into the pacemaker cells. The fourth through eighth components probably do not exceed a few hundredths of a second;[6] the difference between the latency between P-P response on vagal stimulation at the neck and direct stimulation of the vagal endings in the sinus node was only 0.02 second.[6] The ninth component requires the longest of all the components. The latency between vagal stimulation and the first effect on P-P has been found to be 0.1 to 0.2 second, while the interval to the maximum effect on P-P was about 0.4 sec.[6] When two successive stimuli were applied 0.39 second apart, the interval from the first stimulus to the point of maximum effect was 0.9 second.[7] The summation of stimuli from the pressoreceptors acting throughout the peak of the arterial pulse wave may very well lead to intervals of equal or greater length. When the pressure in the carotid sinus of the dog was raised abruptly, the latency before the first effect on the heart rate was 0.3 to 0.5 second, while the latency of the maximal effect was in the order of 2 to 3 seconds.[1] We see, therefore, that the long intervals from the beginning of QRS to the maximum effect on the P waves are quite consistent with the assumption of a vagal reflex activated by the pulse wave.

During transitions from normal A-V conduction to 2:1 block (group A of section 2), the P-P interval immediately preceding a P-P interval without QRS was about 4 per cent longer than the P-P interval following this interval. Both intervals contained a QRS complex, and the only difference between them was that the first interval was preceded by a ventricular systole while the second was not. We can conclude, therefore, that the presence of a normal ventricular systole caused an increase in the following P-P interval, terminated by a P wave appearing about 1.10 second after the QRS complex of this systole. This is consistent with the vagal reflex mechanism as a cause of the negative chronotropic effect. When 2:1 conduction interrupted by ventricular extrasystoles was re-established (group A of section 3), the first P-P with QRS after the extrasystole was only 0.86 per cent longer than the first P-P with QRS after a P-P interval without QRS. This means that a ventricular extrasystole causes a much smaller prolongation of the P-P interval following it

that a normally conducted ventricular systole. This is in keeping with the fact that extrasystoles usually have a smaller stroke volume than regular systoles.

During disappearance of 2:1 A-V block (group B of section 2), the first P-P interval after a P-P interval not containing QRS was about 90 per cent of this latter interval, while the second P-P with QRS was about 97 per cent of this interval. This means that the P-P interval which followed the first systole after the P-P interval without QRS was about 8 per cent longer than the P-P interval following the P-P interval without QRS. Both P-P intervals contained a QRS complex, and the only difference between them was that one of them was preceded by a ventricular systole while the other one was not. We can conclude that in this case ventricular systole exerted a negative chronotropic effect of about 8 per cent on the P-P interval following it. This effect is twice as big in this case as in the case of group A, discussed in the preceding paragraph; the reason for this is that in group B the pause preceding the ventricular systole in question was twice as long as in group A, and the stroke volume as well as the vagal effect caused by it were greater. When ventricular extrasystoles appeared in 2:1 block (group B of section 3), the first P-P interval with QRS after a P-P interval without QRS was about 7 per cent shorter than this latter interval, while the second P-P interval with QRS was only about 6 per cent shorter. The second P-P interval with QRS, which was preceded by a ventricular extrasystole, was accordingly about 1 per cent longer than the first P-P interval with QRS, which was not preceded by ventricular systole. The ventricular extrasystole in this case had a negative chronotropic effect of only 1 per cent (compared with 8 per cent for the normal systole); this could be explained by a smaller stroke volume of the extrasystole.

The effect of atropine or exercise described in section 4 has led us to the conclusion that the negative chronotropic effect disappears or is greatly diminished under these circumstances. This is perfectly in keeping with a vagal reflex nature of this effect, since both atropine and the vagal inhibition appearing after exercise would be expected to interfere with vagal reflexes. That the increased heart rate in itself is not responsible for the inhibition of the negative chronotropic effect is shown by the fact that this effect is fully developed in paroxysmal auricular tachycardias with 2:1 A-V block, where the auricular rates are even faster than those appearing after atropine or exercise. That it is a negative chronotropic and not a positive chronotropic effect which is responsible for the effect of ventricular systole on P-P intervals in paroxysmal tachycardia is shown by the observation mentioned in section 5, that in 3:1 block the P-P interval containing a QRS complex has the same duration as the preceding P-P interval not containing QRS. Furthermore, we shall see that in these cases the P wave terminating the P-P interval containing QRS comes too early after QRS to be influenced by the positive chronotropic effect.

It is commonly believed that contrary to its action on sinus rhythm, the vagus has no slowing effect on auricular ectopic rhythms but rather causes them to terminate abruptly. However, a slowing of the ectopic rate previous to conversion was found in 12 of 33 instances during the conversion to a normal mechanism of supraventricular tachycardias by carotid sinus stimulation.[16] We have observed the same phenomenon also during the conversion of supraventricular tachycardias by ocular pressure. A negative chronotropic effect of ventricular systole was observed by Scherf and his coworkers[34] in auricular ectopic tachycardias caused by topical application of aconitine, when A-V block was produced by vagal stimulation. It was emphasized that the P-P interval containing a QRS complex was of normal duration, while the following interval was prolonged. The authors conclude that a short reflex vagal stimulation may accordingly slow the ectopic stimulus formation in the auricle while a more prolonged direct vagal stimulation often leads to an increase of the ectopic auricular rate.

It must be mentioned that the P wave terminating the prolonged P-P interval which does not contain QRS appears 0.39 to 0.46 second after QRS, at a time when the vagal effect was not yet apparent in cases of A-V block with normal sinus rhythm (table 3). In order to identify the negative chronotropic effect in paroxysmal tachycardia with the vagal effect of the pulse wave, we must assume that the latency of the latter decreases with

an increase of the ventricular rate. Table 3 shows actually that the longest latency of the negative chronotropic effect was found with the slowest ventricular rate (case 1 of the table), while the shortest latency occurred in case 8, which showed the highest ventricular rate; to be sure, the values between these two extremes showed considerable irregularity. One of the major components of the latency period is the duration of ventricular systole, and this shows a marked dependence on the heart rate. In the dog, the latency period of the effect of vagal stimulation on P-P was found shorter when the sympathetic nerves were stimulated at the same time.[6] We might also expect an increase in the conduction velocity of the pulse wave at the high diastolic arterial blood pressures found in paroxysmal tachycardia.

One peculiarity of the effect of ventricular systole which was found in the case of table 2 under the influence of atropine was the appearance of a dip in the curve of P-P intervals at about 0.90 second after beginning of QRS. A corresponding dip was found in the dog when the vagus was stimulated after injection of atropine, but it was often present also under normal conditions; a satisfactory explanation of this double summit type of curve could not be given.[6]

2. Inhibition of the Bainbridge Reflex by a Decrease of the Atrial Pressure Consequent to Ventricular Contraction

Parsonnet and Miller[25] suggested that ventricular systole causes a decrease of auricular pressure with a consequent inhibition of the Bainbridge reflex and an increase of the P-P intervals, while in the following period of ventricular asystole the increased auricular pressure would cause progressive decrease of P-P. This mechanism would apply primarily to the progressive decrease in the P-P intervals which is generally observed during long periods of asystole in Adams-Stokes syndrome, where progressive increase of venous and auricular pressures is likely. However, even in these cases the progressive fall in the arterial blood pressure would be sufficient to account for the decrease of P-P. It is interesting that even in cases of long asystole the first P-P interval following the last ventricular systole is prolonged (e.g., in fig. 3 of reference 31). In a dog in which 2:1 A-V block showing the characteristic alternation of the P-P interval happened to appear during registration of the ventricular and auricular pressures,[21] the latter showed a slight rise toward the end of ventricular contraction and a greater fall immediately after the end of ventricular systole. It is possible that this fall could have caused an inhibition of the Bainbridge reflex and a subsequent increase of the P-P interval not containing QRS, which was terminated by a P wave appearing 0.78 second after this fall in auricular pressure. (The interval would have corresponded well to the latency time of the reflex.) Carlsten and Rudhe,[8] who registered the roentgenkymogram of the right auricular border in cases of complete A-V block, found that the P waves which occurred during ventricular systole and were followed by long P-P intervals were accompanied by auricular waves of greater amplitude and duration than P waves, which appeared later in diastole and were followed by short P-P intervals. These authors suggested that, "Hemodynamic factors (the degree of filling and emptying of the right auricle) might play some role in the mechanism of the arrhythmia", but could reach no definite conclusions. If increased amplitude of auricular contraction is taken to indicate increased auricular pressure during ventricular systole, this observation would be in keeping with the explanation of the arrhythmia by the Bainbridge reflex.

The Bainbridge reflex has been thought to be elicited by pressoreceptors located in the superior vena cava and right auricle, the stimulation of these receptors by increased right auricular pressure causing a reflex vagal inhibition leading to an increase of the heart rate. However, an increase of heart rate on stimulation of these areas was found to be very inconstant and often completely lacking.[3, 36] A group of discharges was found in the vagal nerves which appeared at the beginning of ventricular diastole and were parallel in their intensity to right auricular pressure,[24, 32] but stimulation of the nerves showing these discharges did not lead to an increase of the heart rate.[32] The question of the existence of the Bainbridge reflex is therefore still open; while there is the possibility that this reflex might play a role in the auricular arrhythmia in A-V block, there is no direct proof of this role. At present all observations concerning the negative chronotropic effect of ven-

tricular systole can be explained by the vagal reflex originating in the arterial pressoreceptors.

3. Increased Blood Flow in the Sinus Node as a Consequence of Ventricular Systole

It was suggested that an increase in the blood flow in the arteries supplying the sinus node, consequent to ventricular systole, might cause a better diffusion of metabolites exerting a stimulating action on this node, resulting in a slowing of the auricular rate.[15] We shall discuss the probability of such a mechanism later; however, the long latency of the negative chronotropic effect of ventricular systole as well as its inhibition by atropine would make such a mechanism appear very improbable.

B. The Positive Chronotropic Effect of Ventricular Systole

1. Direct Action of Ventricular Systole on the Pacemaker of the Sinus Node

a. Mechanical Effects of Ventricular Systole. *1. Deformation of the auricle by the ventricular contraction:* Wilson and Robinson[41] suggested, as an alternative to their explanation of the effect of ventricular systole on auricular rhythm in A-V block as a vagal effect, that the mechanical effect of ventricular contraction may hasten the discharge of the normal auricular pacemaker. This explanation was expanded by E. Doumer,[12] who considered that the torsion of the ventricle during its ejection phase may exert a traction on the right auricle and the region of the sinus node. It has been known for a long time that traction, stretching and other mechanical effects increase the irritability of the myocardium and accelerate the stimulus formation; this was confirmed recently by Scherf and his coworkers[35] in the case of auricular tachycardias caused by injection of aconitine. It was found, furthermore, that stretching caused the appearance of negative prepotentials and spontaneous rhythms in Purkinje fibers which had previously shown neither of these phenomena.[39] A similar mechanical effect of the auricular contraction on the ventricle has been used to explain some forms of the Wolff-Parkinson-White syndrome.[20]

The most striking demonstration of the role of the mechanical effect of ventricular contraction on auricular rhythm in A-V block was made by Segers[37] in the case of isolated frog hearts perfused with Ringer solution, in which A-V block was produced by temporarily ligating the A-V groove. Under these conditions it was often observed that auricular contractions occurring during ventricular systole appeared after short intervals while those occurring in the early phase of diastole appeared after long intervals. It could be directly observed that each ventricular contraction caused a distension of the auricle while after the end of ventricular contraction there was a marked decrease in the degree of auricular distension. The fact that this phenomenon was not present when the heart was empty would lead to the conclusion that mechanical and not electrical effects of ventricular systole were responsible for it.

A direct mechanical effect of ventricular systole on the auricle would offer the best explanation for the cases of A-V block reported by Scherf[33] in which the short P-P intervals containing QRS were terminated by P waves showing an aberrant configuration; in one of these cases with Wenckebach's periods only the P waves occurring immediately after ventricular systole were aberrant while the two P waves occurring later during diastole were identical in their configuration. Scherf points out that these aberrant P waves can be easily mistaken for blocked auricular extrasystoles. The case of Perrin[28] showed at first auricular extrasystoles, of the same form as the normal P waves, appearing with fixed coupling intervals in bigeminal rhythm. On another occasion, these extrasystoles were no longer conducted to the ventricle, leading to an electrocardiographic pattern which could not be distinguished from 2:1 A-V block with alternating P-P intervals. Perrin considers that in other cases of A-V block showing anticipation of the P waves occurring during ventricular systole, these P waves represent in reality sinus extrasystoles caused by the mechanical effect of ventricular contraction.

Of the 10 cases contained in table 3, four showed a sudden dip with a more gradual rise in the curve of the P-P intervals. In cases 8, 9 and 10 of this table, the beginning of this dip

was at an interval of about 0.15 to 0.30 second and the maximum at an interval of 0.35 to 0.45 second after beginning of QRS. In general the dips seem to occur earlier when the ventricular rate is higher. The end of the T wave, which coincides approximately with the end of the ventricular ejection phase, occurred in all these cases 0.40 to 0.50 second after the beginning of QRS. As the maximum effect of ventricular traction on the auricle would be expected to occur toward the end of the ejection phase, the time of appearance of the positive chronotropic effect in these cases would be compatible with a mechanical genesis of this effect. It must be emphasized that such an effect would not be expected to have any period of latency in its influence on the stimulus formation. The case of 3:1 A-V block mentioned by Perrin,[28] in which the first P-P interval after ventricular systole was short while the other two intervals were equally long, is also compatible with a mechanical origin of the positive chronotropic effect of ventricular contraction.

During appearance of 2:1 A-V block (group A of section 2), the last P-P interval containing QRS was 6.7 per cent shorter than the following P-P interval which did not contain QRS. Both these intervals stood under the vagal effect of the ventricular systole which had occurred about one second earlier, and the only difference between them was that the P wave terminating the first P-P interval was immediately preceded by ventricular systole while the P wave terminating the second interval was not. In this case we can conclude that the presence of a normal ventricular systole caused the P-P interval terminated by a P wave occurring about 0.40 second after QRS to become about 7 per cent shorter. If we apply the same reasoning to group A of section 3, we find that a ventricular extrasystole had a shortening effect of about 11 per cent in a different case.

During disappearance of 2:1 A-V block (group B of section 2), the second P-P interval following the last P-P interval without QRS was about 3 per cent shorter than this latter interval. During both intervals the vagal influence of the ventricular systole which preceded them was present, and the only difference between them was that the second interval included ventricular systole while the first interval did not. This means that the second normal ventricular systole after the last pause of 2:1 A-V block exerted a positive chronotropic effect of about 3 per cent. We have seen that the first P-P interval containing QRS after this pause was about 10 per cent shorter than the P-P interval without QRS immediately preceding it. As the former was not influenced by the negative chronotropic effect of a preceding ventricular systole while the latter was not influenced by the positive effect of any systole, the difference of 10 per cent is the sum of the positive and negative chronotropic effects. Earlier, in *A 1*, we found that the negative chronotropic effect of the first ventricular systole after a long pause was 8 per cent. By subtracting this amount from the total effect of 10 per cent, we can obtain the positive chronotropic effect of the first ventricular systole following the pause of 2:1 block, which in this case is 2 per cent. We see therefore, that the positive chronotropic effect of a ventricular systole occurring at normal rates is 6 per cent, while this effect is only 2 per cent for the systole following a long pause and 3 per cent for the next systole. We can explain this difference in terms of the mechanical genesis of the positive chronotropic effect if we refer to roentgenkymographic observations which indicate that the volume of the ventricle at the end of systole is greater when the heart rate is low than when it is high, as for instance after exercise.[30] If the ventricular ejection is more complete at high than at low heart rates, we would expect that its mechanical effect on the auricles would also be greater after a long diastolic pause. That this positive chronotropic effect was still small in the second systole following the pause might be explained by a staircase effect. The observation mentioned in the previous paragraph, that the positive chronotropic effect was greater in ventricular extrasystoles than in normal beats, might also be explained by a deficient filling and consequently a more complete emptying of the former.

The assumption that the mechanical effect of

ventricular contraction on the auricle is greatest after short ventricular pauses would also be in keeping with our observation that the positive chronotropic effect of ventricular systole was present especially in the cases with a high ventricular rate (table 3). In case 4 of this table, this effect was greater, while the negative chronotropic effect was smaller, when the ventricular rate was higher.

After atropine or exercise, the negative chronotropic effect of ventricular contraction was found to be absent or greatly diminished, while the positive chronotropic effect seemed to be approximately the same or even greater. In our case of complete A-V block this effect was 7 per cent before and after atropine, while in our case of 2:1 block the calculated effect at rest was about 2 per cent while the effect after exercise was about 5 per cent. This is in keeping with the mechanical genesis of the positive chronotropic effect, which could not be expected to be influenced by vagal inhibition. As far as our observation in cases of auricular tachycardia with 2:1 A-V block are concerned, we have already mentioned that the auricular arrhythmia in these cases seems to be due entirely to a negative chronotropic effect of ventricular systole. One of the reasons for this may be that the P waves in these cases always occurred outside of the period (around 0.35 second after QRS) where a maximum positive chronotropic effect would be expected.

2. Direct effect on the sinus node of auricular pressure changes caused by ventricular systole: It has been suggested that changes in the auricular pressure exercise a direct effect on the rate of stimulus formation in the sinus node.[32-36] since they may cause changes of the auricular rate even in denervated hearts.[38] The increase of auricular pressure during ventricular systole, which was referred to earlier during the discussion of the Bainbridge reflex, might accordingly cause a direct shortening of the P-P intervals. We would expect this positive chronotropic effect to appear at about the same time as a direct mechanical effect of ventricular contraction. However, the observations quoted during the discussion of the Bainbridge reflex, in which an increase of auricular rate failed to appear even after considerable increase of auricular pressure would make it improbable that such a mechanism operates under the very small changes of auricular pressure occurring during ventricular systole. At any rate, the traction exerted on the sinus node by such changes of auricular pressure would be much smaller than that exerted by the powerful contraction of ventricular muscle.

b. Direct Effect of the Electrical Activity of the Ventricles on the Sinus Node. It is well known that direct electric currents cause at the cathode an acceleration of existing rhythmic activity or even the appearance of automatism when it was not present previously. Segers[37] has shown that two frog hearts or myocardial fragments can synchronize themselves when the action potentials of one can reach the other. If the negative action potential appears just before the stimulus is discharged, it can accelerate the latter, but if this potential appears shortly after the discharge has taken place, it will fall into the refractory phase and remain without effect, while the postcathodic depression which follows it can delay the appearance of the next discharge.[37] Schaefer[32] suggested that an accelerating effect of the action potential of the ventricles on the auricle might be responsible for the varying P-P intervals in A-V block. An effect of this kind could be produced either by the ventricular QRS complex or by the T wave, both of which have normally a predominantly negative potential in leads from within the right auricle,[20] and in lead aV_R which shows greatest resemblance to the latter. The QRS complex has the greater voltage, while the T wave has the greater duration. As in the case of the mechanical effect of ventricular contraction, the electrical effect would be expected to act without any latency. If the QRS complex were responsible for the chronotropic effect, the maximum of this effect would appear very early after QRS; this did not happen in our cases. If the T wave were responsible for the electrical effect, the time of appearance of this effect would be the same as in the case of a mechanical effect. It would favor an electrical mechanism if the presence or absence of a positive chronotropic effect depended on the voltage and direction of the ventricular com-

plex in lead aV_R, but no such relation could be found in the material accessible to us. On the other hand, the dependence of the positive chronotropic effect on the preceding ventricular pause which we mentioned earlier would definitely favor a mechanical genesis of this effect.

c. Increased Blood Flow in the Arteries of the Sinus Node During Ventricular Systole. Wenckebach and Winterberg[40] explained the auricular arrhythmia in A-V block by assuming that the increased blood flow in the arteries supplying the sinus node during ventricular systole resulted in improved nutrition of this node and accelerated stimulus formation. Two conditions would have to be fulfilled if this assumption were valid. First of all, a phasic blood flow not only in the arteries but also in the capillaries of the sinus node would have to be assumed. While such a pulsatile flow is usually absent in the capillaries it may appear under certain conditions, such as vasodilatation and high pulse pressure.[18, 19] The pulse pressure in the coronary arteries, which are the first to originate from the aorta, can be expected to attain high values, especially at the slow ventricular heart rates usually present in A-V block. Although the maximum flow in the coronary arteries occurs in the diastole, the arteries supplying the auricles would be expected to have a systolic flow maximum, as the auricles are relaxed at this time. However, even if phasic blood flow were present in the capillaries of the sinus node, it is unlikely that the amount of oxygen reaching the interior of the muscle fibers would show considerable variations of this kind because of the diffusion gradient. At any rate, this gradient would delay the maximum oxygen supply at least until late systole, and this would be inconsistent with the early maxima of the positive chronotropic effect observed in some of our cases. The second assumption is that the rate of stimulus formation in the sinus node is actually dependent on its blood supply. While a depression of stimulus formation does appear in extreme anoxia, it is unlikely that such a condition should exist in the sinus node during diastole. Furthermore, our observations indicate that the positive chronotropic effect of ventricular systole is more marked at high than at low ventricular rates, and pulsatile flow in the capillaries of the sinus node would be less likely under these conditions.

2. Reflex Mechanisms as a Cause of the Positive Chronotropic Effect of Ventricular Systole

a. The Bainbridge Reflex. We have already discussed the possible role which the Bainbridge reflex may play in the genesis of the negative chronotropic effect following ventricular systole. This reflex was considered responsible for the decrease of the P-P intervals during ventricular systole,[25] but in view of the fact that this reflex would necessarily require a considerable period of latency, it can not be applied to explain the early positive chronotropic effect of ventricular systole described in this paper. The persistence of this effect after atropine or exercise is also incompatible with a vagal reflex mechanism.

b. Pulmonary component of the Bainbridge Reflex. It was suggested[3] that the auricular acceleration attributed to the Bainbridge reflex may result from stimulation of pressoreceptors located in the pulmonary artery. Discharges originating in such receptors have been observed to occur synchronously with the peak of the pulmonary arterial pressure wave.[27] However, the exact effect of these discharges is unknown, and it is improbable that they play any role in the positive chronotropic effect of ventricular systole for the same reasons which have been quoted as opposed to a similar role of the Bainbridge Reflex.

c. Changes in the vegetative nervous tone caused by phasic blood flow in the medulla. It was suggested[9, 10] that the acceleration of blood flow caused by ventricular systole in the vagal centers located in the medulla result in rhythmic changes in the vagal or sympathetic tone through a rhythmic change of oxygenation and carbon dioxide removal. Such changes of the reflex tone, even if present, would not be of use in an explanation of the positive chronotropic effect of ventricular systole for the reasons listed during our discussion of the role played by the Bainbridge Reflex.

The dip in the curve of P-P intervals in case 4 of table 3 as well as the second dip in case 9

c this table occurred 0.65 to 0.85 second after t e beginning of QRS and about 0.40 second a ter the end of the T waves. Because of this l ng interval, it is difficult to explain these dips b a direct action of ventricular systole on the a ricular stimulus formation. The best ex- p anation at present would be that they were c used by one of the reflex mechanisms d scribed in this section. This conclusion would b supported by the observation that in case 4 o table 3 the P-P intervals became constant a ter atropine, but in this case the disap- p arance of the chronotropic effect could have b en only an apparent one, as pointed out in s ction 4.

Conclusions

The observations presented in this paper have led us to the conclusion that each ventricular systole may exert even under normal conditions two distinct effects on the stimulus formation in the auricles. The first is a positive chronotropic effect, which tends to accelerate the stimulus formation and has a maximum effect on P waves appearing 0.3 to 0.4 second after the beginning of the ventricular QRS complex. It is more pronounced at moderate than at slow ventricular rates and is probably caused by the traction of the contracting ventricle on the right auricle. In some published cases, which we were unable to investigate in detail, this effect occurred 0.60 to 0.85 second after beginning of QRS, and was probably mediated by a nervous mechanism related to the Bainbridge reflex. The second effect is a late negative chronotropic effect which appears 0.6 to 1.00 second after the beginning of QRS, is more pronounced at slow ventricular rates, and is very probably due to a reflex vagal stimulation caused by arrival of the pulse wave at the arterial pressoreceptor areas. In the normal range of heart rates, these two effects probably neutralize each other, as each sinus discharge is under the influence of the positive chronotropic effect of the preceding ventricular systole and of the negative chronotropic effect of the systole preceding the latter. At high heart rate the sinus rhythm is influenced more by the positive chronotropic effect of the preceding systole, while at low rates the negative chronotropic effect predominates. This interaction may explain the observation of Schaefer[32] that the frequency distribution of P-P intervals in certain cases of respiratory arrhythmia shows pronounced maxima at the values of 0.7 and one second, while the values around 0.85 second may not appear at all. The assumption could be made that P waves which would be due to appear at these latter intervals would either appear prematurely because of a positive chronotropic effect of the preceding systole or appear delayed because of a negative chronotropic effect.

In A-V block, P-P intervals containing a QRS complex are terminated by P waves which are usually affected by the positive chronotropic effect of the preceding ventricular systole and are accordingly shorter than P-P intervals which do not contain QRS and are terminated by P waves appearing under the influence of the negative chronotropic effect. This interaction tends to delay P waves which normally would have appeared during the second half of diastole and to accelerate P waves which otherwise would have appeared during the first half of diastole; as a result, most P waves in complete A-V block showing pronounced chronotropic effects of ventricular systole appear either shortly before the QRS complex or soon after the T wave. This accounts for the well known observation that some cases of complete A-V block may show an electrocardiographic pattern closely resembling 2:1 block for long periods of time. Figure 3a shows such a synchronization of the auricles and ventricles in the absence of true A-V conduction.

Under certain conditions the usual relation between QRS complexes and P-P intervals may be reversed, so that P-P intervals containing QRS are longer than those not containing it. Such a paradoxic behavior of the P-P intervals can be brought about by two factors. The first of these includes sudden variations of the auricular rate caused by changes of the sympathetic or vagal tone not related to ventricular systole. If these variations are greater than those caused by the chronotropic effect of ventricular systole, a paradoxic behavior of P-P may appear. The second factor depends on the time of appearance of the P waves ter-

minating P-P intervals enclosing a QRS complex. If the positive chronotropic effect of ventricular systole predominates, P-P intervals terminated by P waves which appear before this effect has developed, that is, within 0.15 to 0.35 second of the beginning of QRS, will not be affected, while the following P-P intervals will be shortened although they do not contain a QRS complex, since the P waves which terminate them will appear during the positive chronotropic effect. In complete A-V block, where the P waves may appear at any time after QRS, a certain percentage of P-P intervals will accordingly always be paradoxic. In table 3, this was true of the cases 4, 8 and 9 in which all paradoxic P-P intervals were terminated by P waves appearing early after QRS. In case 10 there were no paradoxic P-P intervals in spite of the fact that the positive chronotropic effect predominated, since the auricular rate was very slow and the following P waves were already influenced by the slight negative chronotropic effect present in this case. The same explanation applies to those instances of cases 4 and 8 of the table where P-P containing QRS did not show a paradoxic behavior even when it was terminated by a P wave appearing very soon after QRS.

In cases of complete A-V block in which the late negative chronotropic effect of ventricular systole predominates, the P-P interval containing QRS is usually influenced by this effect much less than the following interval, and accordingly shows no aberrant behavior (cases 5 and 7 of table 3). However, if the auricular rate is low, P waves which appear a short time before a QRS complex may initiate P-P intervals which contain QRS but are longer than the average because the P waves terminating them will be already under the influence of the negative chronotropic effect; these P-P intervals will accordingly show a paradoxic behavior. On the other hand, if the P-P intervals become even longer, nearly every P-P interval will contain a QRS complex, and the term "paradoxic behavior of P-P" can then be applied only in rare instances. Another type of paradox may appear if the ventricular rate is very low compared with the auricular rate and the negative chronotropic effect is late; in this case the P-P intervals containing QRS will be still influenced by the negative chronotropic effect of the preceding ventricular systole, while during the following P-P interval this effect will have declined considerably while the negative chronotropic effect of the systole which has just terminated will not have commenced yet. In this case the paradoxic P-P intervals are terminated by P waves which appear within comparatively short intervals of QRS, as in case 1 of table 3.

It is the current belief that atropine abolishes the effect of ventricular systole on auricular rhythm in A-V block, as manifested by the difference in the P-P intervals containing and those not containing QRS complexes. Our observations show that a disappearance of this difference may be only a transitional phase appearing previous to complete reversal of this difference. The cases in which such a reversal was observed showed a predominant positive chronotropic effect of ventricular systole, and the reversal in these cases was caused by two factors. The first of these was the disappearance of the vagal negative chronotropic effect, while the second was an acceleration of the auricular rate which caused the P waves following the P-P intervals with QRS to appear during the maximum of the positive chronotropic effect. The latter was not influenced by atropine. It is probable that in cases of A-V block in which the negative chronotropic effect of ventricular systole is the only one present the disappearance of the effect of ventricular systole on P-P would be a genuine one, and no reversal of the effect would be observed. The same considerations would apply to the effect of exercise.

In cases of 2:1 A-V block with a predominant positive chronotropic effect, a paradoxic behavior of the P-P intervals is likely to appear, if the P-R intervals are long, and cause the next P wave to appear soon after QRS. On the other hand, in cases with a predominant negative chronotropic effect, in which the heart rate is usually low, a paradoxic behavior of P-P is likely to appear if the P-R interval is short, thus allowing the blocked P wave to appear under the influence of the maximum negative chronotropic effect. Between the values of P-R which lead to the usual and those which lead

to a paradoxic behavior of the P-P intervals, a value can be found at which the effect of ventricular systole on P-P intervals will be apparently entirely absent. It is very likely that among the cases of A-V block listed in the introduction as not showing such an effect, many would have shown this effect at a different heart rate. In addition to these, there are certainly many cases which show a true absence of the chronotropic effect of ventricular systole; in such cases this effect is absent also when the degree of block changes or when complete A-V block appears. Some of the factors which may be responsible for this lack of a chronotropic effect of ventricular systole have been enumerated by Roth and Kisch;[31] the evaluation of these factors would need a more extensive material than is available in the present paper.

Summary

1. In one personal and nine published cases of complete A-V block, which showed a pronounced difference between P-P intervals containing a QRS complex and those not containing it, the relation between the P-P intervals and the time of appearance of the P waves concluding them with respect to the beginning of QRS was plotted in graphic form. In six of these cases, the curve of P-P intervals showed a sudden rise 0.7 to 1.7 second after beginning of QRS, followed by a gradual return to the initial values. These cases were considered to show only a negative chronotropic (i. e. slowing) effect of ventricular systole on the auricular rate. One case showed a sudden dip in the curve of P-P intervals at about 0.15 to 0.30 second from the beginning of QRS, followed by a gradual return to initial values; this case was considered to show only a positive chronotropic (i. e. accelerating) effect of ventricular systole. Three cases showed both an early dip and a late rise in the curve of P-P intervals; these cases were considered to show both a positive and a negative chronotropic effect.

2. In one case of transient 2:1 A-V block, the behavior of the P-P intervals were studied during these transitions. From the effect of the absence of a ventricular systole on the P-P intervals, the values of the positive and negative chronotropic effects of this systole and of the following systole were calculated. The same procedure was applied to a case of complete A-V block in which the ventricular pauses were sometimes interrupted by ectopic ventricular beats.

3. The effect of atropine and of exercise was studied in two cases of A-V block. While at rest these cases showed that P-P intervals containing QRS were usually shorter than those not containing it, atropine or exercise causes this difference at first to disappear and later to become reversed. This behavior was explained by assuming that the positive chronotropic effect of ventricular systole was not influenced by atropine while the negative chronotropic effect disappeared.

4. In one personal and 15 published cases of auricular paroxysmal tachycardia with 2:1 A-V block, the P-P intervals containing a QRS complex were shorter than those not containing it. The fact that this behavior was present at the same auricular rates at which the reverse behavior appeared in simple A-V block after atropine or exercise was explained by the persistence of the negative chronotropic effect of ventricular systole in paroxysmal tachycardia.

5. Seven possible explanations of the positive chronotropic effect of ventricular systole were discussed; the most probable one is that this effect is caused by an accelerated stimulus formation in the sinus node under the influence of the traction exerted by the contracting ventricle on the right auricle. Three possible explanations of the negative chronotropic effect of ventricular systole were discussed; the most probable one is that this effect is caused by a reflex vagal slowing of the sinus rhythm as a result of the stimulation of arterial pressoreceptors by the pulse wave.

6. It is probable that in normal rhythm the positive chronotropic effect of ventricular systole on the sinus node is approximately counterbalanced by the negative chronotropic effect of the preceding systole. In A-V block the positive chronotropic effect of ventricular systole usually causes the P-P intervals containing a QRS complex to be shortened while the negative chronotropic effect causes the P-P intervals not containing QRS to be prolonged. Under certain circumstances a paradox in the

behavior of the P-P intervals may appear, causing the reversal of this difference. In cases showing a predominant positive chronotropic effect this is likely to appear when P waves concluding a P-P interval containing a QRS complex appear very soon after the QRS complex, before this effect has had time to appear. In cases showing a predominant negative chronotropic effect a paradoxic behavior of P-P may appear also when the P waves terminating it fall soon after QRS, since then the following P waves appear at the maximum of the negative chronotropic effect. When the auricular rate is slow, paradox P-P intervals tend to appear when the P waves terminating them are midway between two QRS complexes. If the P waves happen to appear at a position between that favoring a normal behavior of P-P with respect to QRS, and that favoring a paradoxic behavior, an apparent absence of the effect of ventricular systole on P-P may result

Summario in Interlingua

In alicun casos de complete bloco auriculo-ventricular, le curva del duration de intervallos P-P exhibiva un subite descendita con un sequente restitution gradual durante e post le unda T. Iste positive effecto chronotropic (effecto accelerante) del parte del systole ventricular es probabilemente causate per le traction que le contrahente ventriculo exerce super le auriculo dextere. Altere casos exhibiva subite ascenditas in le curva del intervallos P-P verso le fin del diastole. Hic le restitution esseva etiam gradual. Iste negative effecto chronotropic (effecto retardante) es probabilemente causate per un reflexo vagal que resulta del stimulation del pressoreceptores arterial per le unda del pulso. Le interaction de iste duo effectos determina si le intervallos P-P que contine QRS va esser plus breve que illos que non contine QRS o si iste relation es le contrario (effecto paradoxe).

Acknowledgment

Unless otherwise specified, the original electrocardiograms presented in this paper were taken from the files of the Pabellón de Cardiología Luis H. Inchauspe, Buenos Aires, Argentina. We should like to thank Dr. Blas Moia, Director of this Institute, for permission to use them.

BIBLIOGRAPHY

[1] Alvarez, Buylla, R.: Influencia de la actividad de los baroreceptores del seno carotideo, sobre la frecuencia cardiaca. Arch. Inst. cardiol. México. **21:** 111, 1951.

[2] Ashman, R. and Gouaux, J. L.: Reflex inhibition of the human heart. Complete A-V block and parasystole. Proc. Soc. Exper. Biol. and Med. **37:** 25, 1937.

[3] Ballin, I. R. and Katz, L. N.: Observations on the localization of the receptor area of the Bainbridge reflex. Am. J. Physiol. **135:** 202, 1941.

[4] Barker, P. S., Wilson, F. N., Johnston, F. D., and Wishart, S. W.: Auricular paroxysmal tachycardia with auriculoventricular block. Am. Heart J. **25:** 765, 1943.

[5] Barker, P. S., Johnston, F. D., and Wilson, F. N.: Auricular paroxysmal tachycardia with alternation of cycle length. Am. Heart J. **26:** 799, 1943.

[6] Brown, G. L. and Eccles, J. C.: The action of a single vagal volley on the rhythm of the heart beat. J. Physiol. **82:** 211, 1934.

[7] Brown, G. L. and Eccles, J. C.: Further experiments on vagal inhibition of the heart beat. J. Physiol. **82:** 242, 1934.

[8] Carlsten, A., and Rudhe, V.: An electrokymographic study of auricular arrhythmia in total heart block. Acta Radiol. **41:** 316, 1954.

[9] Condorelli, L.: Quoted in reference 10.

[10] Corsi, V.: Osservazioni sulla influenza della sistole ventricolare sul ritmo sinurale. Minerva med. **1:** 966, 1950.

[11] Decherd, G. M., Herrmann, G. R., and Schwab, E. H.: Paroxysmal supraventricular tachycardia with A-V block. Am. Heart J. **26:** 446, 1943.

[12] Doumer, E.: Quoted in reference 10.

[13] Fatzer, G.: Quoted in reference 10.

[14] Garten, J.: Über die Abhängigkeit des Sinusrhythmus von der Kammertätigkeit bei A-V Dissoziation. Zeitschr. ges. inn. Med. **8:** 65, 1953.

[15] Graybiel, A. and White, P. D.: Complete auriculo-ventricular dissociation. Am. J. M. Sc. **192:** 334, 1936.

[16] Hellerstein, H. K., Levine, B., and Feil, H.: Electrocardiographic changes following carotid sinus stimulation in paroxysmal supraventricular tachycardia. J. Lab. and Clin. Med. **33:** 820, 1951.

[17] Kisch, B.: Beobachtungen bei einem Kranken mit totalem Block. Cardiologia **2:** 47, 1938.

[18] Krogh, A.: The Anatomy and Physiology of Capillaries. New Haven: Yale University Press, 1936.

[19] Landis, E. M.: Capillary pressure and capillary permeability. Physiol. Reviews **14:** 404, 1930.

[20] Lepeschkin, E.: Modern Electrocardiography

Baltimore, Williams and Wilkins Company, 1951, Volume I.

[21] ITTLE, R. C.: Effect of atrial systole on ventricular pressure and closure of the A-V valves. Am. J. Physiol. **166:** 289, 1954.

[22] OWN, B., WYATT, N. F., CROCKER, A. T., GOODALE, W. T., AND LEVINE, S. A.: Interrelationship of digitalis and potassium in auricular tachycardia with block. Am. Heart J. **45:** 589, 1953.

[23] IATSUDA, K. AND TOMONO, H.: Influence of ventricular systole upon cardiac sinus rhythm in man. Tohoku J. Exper. Med. **51:** 366, 1949.

[24] 'AINTAL, A. S.: A study of right and left atrial receptors. J. Physiol. **121:** 182, 1953.

[25] 'ARSONNET, A. E., AND MILLER, R.: Heart block. The influence of ventricular systole upon the auricular rhythm in complete and incomplete heart block. Am. Heart J. **27:** 676, 1944.

[26] 'ARSONNET, A. E., MILLER, R., BERNSTEIN, A. AND KLOSK, E.: Bigeminy. Am. Heart J. **31:** 74, 1946.

[27] PEARCE, J. W. AND WHITTERIDGE, D.: The relation of pulmonary arterial pressure variations to the activity of afferent pulmonary vascular fibers. Quart. J. Exper. Physiol. **36:** 177, 1951.

[28] PERRIN, P.: Extrasystoles sino-auriculaires bloquées realisant une dissociation auriculo-ventriculaire. Arch. mal. coeur **45:** 503, 1952.

[29] RASARIO, G. M.: Quoted in reference 10.

[30] REINDELL, H.: Diagnostik der Kreislauffrühschaden. Ferdinand Enke, Stuttgart, 1949.

[31] ROTH, I. R. AND KISCH, B.: The mechanism of irregular sinus rhythm in auriculo-ventricular heart block. Am. Heart J. **36:** 257, 1948.

[32] SCHAEFER, HANS: Das Elektrokardiogramm: Theorie und Klinik, Heidelberg, Springer-Verlag, 1951.

[33] SCHERF, D.: Periodic changes in the form of the P waves in partial heart block. Am. Heart J. **29:** 213, 1945.

[34] SCHERF, D., BLUMENFELD, S., MUELLER, P., AND BEINFIELD, W. H.: On the response of ectopic auricular tachycardias to vagus stimulation. Am. Heart J. **45:** 95, 1953.

[35] SCHERF, D., SCHARF, M. M., AND GOKLEN, M. F.: Effect of stretch and pressure on stimulus formation in the dog's auricle. Proc. Soc. Exper. Biol. and Med. **70:** 708, 1949.

[36] SCHROEDER, W. AND BREHM, H.: Untersuchungen über den adäquaten Reiz des Bainbridge-Reflexes. Arch. ges. Physiol. **255:** 114, 1952.

[37] SEGERS, M.: Les phenomenes de synchronisation au niveau du coeur. Arch. internat. physiol. **54:** 87, 1946.

[38] TIITSO, M.: Quoted in reference 27, p. 339.

[39] TRAUTWEIN, W. AND GOTTSTEIN, U.: Potentialmessungen am Reizentstehungsort des Herzmuskels. Die Naturwissenschaften **40:** 443, 1953.

[40] WENCKEBACH, K. F. AND WINTERBERG, H.: Die Unregelmässige Herztätigkeit. Leipzig, W. Engelmann, 1927.

[41] WILSON, F. N., AND ROBINSON, A. C.: I. Two cases of complete heart block showing unusual features. Arch. Int. Med. **21:** 166, 1918.

Reflex Venomotor Activity in Normal Persons and in Patients with Postural Hypotension

By E. B. Page, M.D., J. B. Hickam, M.D., H. O. Sieker, M.D., H. D. McIntosh, M.D. and W. W. Pryor, M.D.

Reflex venomotor activity has been observed and measured in normal subjects by means of the pressures developed within isolated segments of superficial veins. Strong contractions are caused by the Valsalva maneuver, tilting, cold, exercise, and hyperventilation. After the Valsalva and after tilting there is a brief elevation of central venous pressure. Pulmonary vascular pressures are also increased after the Valsalva. This is taken to indicate a widespread venoconstriction with central shifting of blood. Persons with postural hypotension show little or no segment or central venous pressure response to these stimuli, indicating impaired reflex venomotor activity.

THE existence of reflex venomotor activity is well established,[1, 2, 3, 4] and it is evidently important in many circulatory adjustments in health and disease. However, there is little quantitative information on venomotor activity in man because it has been difficult to measure. Recently Duggan, Love, and Lyons[5] have introduced the simple technic of measuring pressure changes within a superficial vein segment temporarily isolated by external pressure and have found prompt reflex responses to various stimuli. It is the purpose of this report to extend these observations to include additional stimuli of physiologic significance, and to describe the results of such measurements in persons with orthostatic hypotension. In addition measurements have been made of changes in the central venous pressure with such stimuli to determine to what extent the central venous pressure may reflect changes in peripheral venomotor activity.

Methods

A modification of Duggan's technic was used. This consisted of isolating a superficial venous segment temporarily by applying pressure at the ends of the segment. In this way the volume of the segment was held constant and contraction of the vein was reflected by an increase in pressure. Pressure within the segment was recorded continuously during each experimentally induced contraction.

The limb bearing the vein segment to be tested was supported in a felt-lined trough (fig. 1). Rods along the sides of the trough allowed the adjustment of two yokes which held piston spring clamps. By these clamps the necessary pressure was applied to the ends of the segment. With the arm snugly in place and the clamps tending to press the arm even more firmly into the trough, the unit was very stable and allowed the subject to perform the various test procedures without undue motion of the arm and without obstructing the return of blood through other veins.

For recording intrasegment pressure, a siliconed needle was inserted into the vein. With the object of minimizing trauma and avoiding spasm a small needle was employed, generally size 23. From the needle, stiff polyethylene tubing led to a Statham pressure transducer (range 0 to 75 cm. Hg). Appropriate stopcocks were included in the system to allow convenient checking of the pressure baseline and to permit connecting the system occasionally with a slow drip containing approximately 25 mg. of heparin per liter of saline. The use of heparin in saline did not appear to alter behavior of the vein segment. While the subject was resting between measurements, blood was permitted to flow through the segment. Saline was not introduced into the closed segment during measurements of vein reactivity in order to avoid effects resulting from abnormal blood electrolyte composition.

To obtain satisfactory results it was necessary to use a vein segment without tributaries. Veins with obvious tributaries were not used. A segment that seemed suitable was emptied of blood and then blocked with the fingers. The arm was engorged with a tourniquet to determine whether there would be leaking into the segment. The reverse test was made by engorging the arm with a tourniquet, blocking the segment, and then releasing the tourniquet

From the Department of Medicine, Duke University School of Medicine, Durham, North Carolina.

This work was supported by Contract AF 33(616)-441 monitored by the Aero Medical Laboratory, Wright-Patterson Air Force Base, Dayton, Ohio, and by a grant from the Life Insurance Medical Research Fund.

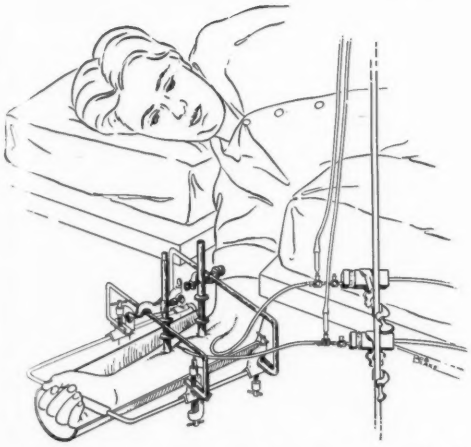


FIG. 1. The arrangement for measuring simultaneously the pressure within a superficial venous segment of the forearm and the central venous pressure.

to determine whether the vein would remain engorged as the surrounding veins collapsed. After the blocks were applied and before each procedure, the segment pressure was continuously measured during a prolonged control period. The control pressure in the vein was always considerably above that of the surrounding veins. After each stimulus saline was allowed to flow into the vein under 60 to 70 mm. Hg pressure until it stopped and finally the stability of this pressure in the distended vein was recorded. Thereafter, the clamps were removed and blood flow was re-established for a time before beginning the next measurement of reactivity.

The central venous pressure (CVP) was recorded by having the subject lie on his side with the dependent arm laterally extended through a hole in the table so that there was an engorged vein from the antecubital fossa to the right atrium (6). An 18 gage needle was inserted into an antecubital vein and connected to a 0 to 5 cm. Hg Statham pressure transducer. The calibrations in centimeters of water on the illustrations are not corrected for the hydrostatic column extending from the pressure transducer to the zero reference point since the chief interest lies in pressure changes and not the absolute central venous pressure.

RESULTS

Normal Superficial Vein Segments

The data on responses of superficial vein segments in normal subjects to the Valsalva maneuver, foot-down tilting, exercise, cold, and hyperventilation are presented in figure 2 and summarized in table 1. Most of these subjects were medical students with an age range of 21 to 30 years. The oldest subject was 56, and his responses were close to the group mean. All subjects were males.

The Valsalva maneuver, which was maintained for 30 seconds at a pressure of 40 mm. Hg, caused more vigorous segment contractions than any other stimulus. The mean pressure rise (16.5 mm. Hg) was significantly greater than that resulting from cold and hyperventilation. With the Valsalva, as with all stimuli, the vein began to contract immediately after the application of the stimulus, but the pressure built up relatively slowly. As shown in figure 3, the segment pressure continued to increase for several seconds after the intrathoracic pressure was released, and it then slowly returned toward the previous level. To preclude the possibility that the general elevation of venous

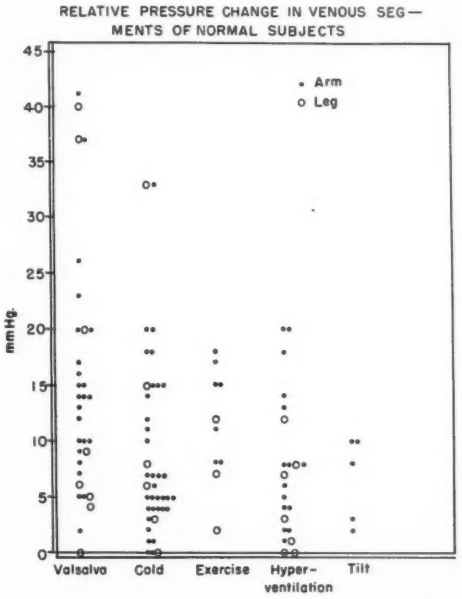


FIG. 2. Increase in pressure within superficial venous segments of normal subjects in response to various stimuli. There were 15 subjects. All stimuli were not applied to each subject. In many instances a particular stimulus was applied several times to a given subject; each response is recorded in the figure. The mean response of the group to each stimulus appears in table 1.

TABLE 1.—*Pressure Response in Normal Arm Vein Segments*

	No. of Observations	No. of Subjects	Mean Pressure* Increase (mm. Hg)	Standard Deviation
Valsalva	32	13	16.5	±8.9
Exercise	11	7	13.4	±5.8
Cold	40	15	8.9†	±4.7
Hyperventilation (60 seconds)	22	11	8.6‡	±4.9

* Mean of each individual's average response.
† Significantly less than response to Valsalva ($p < .01$)
‡ Significantly less than response to Valsalva ($p < .02$)

pressure during the maneuver might force blood into the segment past the obstructing tampons, an arterial cuff at a pressure of 300 mm. Hg was applied around the upper arm above the segment on several occasions. This did not alter the development of pressure within the segment.

Foot-down tilting for 50 seconds also caused the segment to contract, though not so strongly as the Valsalva maneuver. After return to the horizontal position, the segment slowly relaxed. In all tilting experiments the circulation was excluded from the arm by an arterial cuff proximal to the segment.

Exercise, done by alternate flexing and extending the knee and hip of one leg, usually caused a strong segment contraction.

As reported by Duggan, Love and Lyons,[5] segment contractions were also produced by hyperventilation, cold, and apprehension. The cold stimulus was applied by immersing the opposite hand, or a foot, in ice water. A part of the effect of ice water is caused by pain, but cool water, which was not unpleasant, also produced a definite segment contraction. Apprehension alone can cause a strong segment contraction. We were able to repeat Duggan's experiment of inducing a contraction by announcing to the subject that the hand would be immersed in ice water for a prolonged period.

Segment responses of the saphenous vein at the ankle were measured in several subjects (fig. 2). The results were less consistent than with the forearm veins, but very strong contractions were obtained in one subject. The lower saphenous vein has a pronounced tendency to contraction on puncture with a needle, and the persistence of this spasm, which at times was obvious, may have accounted for some of the irregularity in response.

In most instances, repeated measurements were made of segment response to the different stimuli. In certain subjects measurements were made on different days and in different vein segments. These repeated measurements showed considerable variability in the magnitude of the response. As an example, one subject responded to the Valsalva maneuver on six different trials with pressure rises of 13, 15, 7, 18, 20 and 5 mm. Hg. It is apparent that the response of a venous segment as measured by this technic will depend in part on the condition of the vein prior to the stimulus. If the vein is already contracted because of the subject's apprehension or because of local irritation of the vein, the response to a stimulus is likely to be abnormal and may well be reduced. The segment response may also

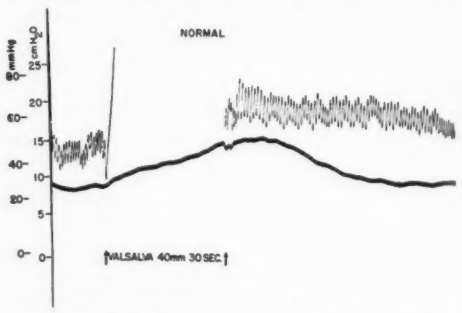


FIG. 3. Simultaneous recording of changes in central venous pressure and in pressure within an occluded segment of a superficial arm vein during performance of the Valsalva maneuver by a normal subject. The upper tracing represents the central venous pressure, and the pressure scale for this tracing is in cm. water. The actual pressure recorded is that of a vein in the antecubital fossa of the dependent arm, but changes in this pressure reflect accurately changes in the central venous pressure. Segment pressure, measured in mm. Hg, is represented by the lower tracing. Note that segment pressure continues to rise for several seconds after release of the Valsalva. The rise in central venous pressure considerably outlasts the pressure rise in the superficial segment.

epend somewhat upon the initial segment ressure, which is caused by application of the umpons and usually amounts to 20 to 40 mm. Hg. In the present study the segment activity expressed as change in pressure, but the total ressure which the segment develops during ontraction might also be used as an index of enous activity. On several occasions total ressures of over 60 mm. Hg were developed n arm segments by the addition of contraction ressure to the initial pressure.

The Normal Central Venous Pressure

The data on responses of the central venous pressure to the Valsalva maneuver, foot-down tilting, exercise, cold, and hyperventilation are presented in table 2 and figure 4.

The greatest increase in central venous pressure was caused by the Valsalva maneuver. Measurements were made in the post-Valsalva period a few seconds after the release of intrathoracic pressure. As shown in figure 3, the central venous pressure remains elevated for a considerable time after the Valsalva. It is usually fairly well sustained for at least 30 seconds, and in most instances it does not completely return to the previous level until more than 120 seconds after release of intrathoracic pressure. The superficial segment pressure subsides much more rapidly (fig. 3). This disparity between the rate of fall of central venous pressure and segment pressure was consistent. Ankle vein segments also relaxed relatively quickly after the Valsalva maneuver, while the central venous pressure continued to be elevated.

TABLE 2.—*Central Venous Pressure Changes in Normal Subjects*

	No. of Observations	No. of Subjects	Mean Pressure Increase (cm. H_2O)*	Standard Deviation
Post-Valsalva	28	9	3.4	±1.3
Cold	18	7	0.3†‡	±0.3
Exercise	10	5	0.4†§	±1.0
Hyperventilation	19	8	0.4†	±2.0
Tilt	13	8	2.1	±1.3

* Mean of each individual's average response.
† Significantly less than response to Valsalva ($p < .01$)
‡ Significantly less than response to tilt ($p < .02$)
§ Significantly less than response to tilt ($p < .05$)

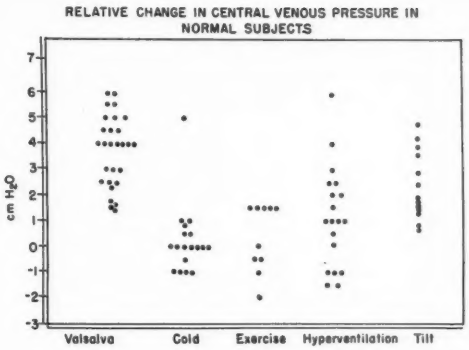


FIG. 4. Change of central venous pressure in nine normal subjects in response to various stimuli. The mean response of the group to each stimulus appears in table 2.

In the tilting experiments, the central venous pressure was measured before and immediately after a 60 degree foot-down tilt of four minutes duration. All measurements were made with the subject in the horizontal position. Tilting caused a consistent increase in central venous pressure, but not as much as the Valsalva maneuver. As with the Valsalva maneuver, the change in central venous pressure caused by tilt persisted after return to the horizontal for a much longer time than did the increase in superficial segment pressure.

Exercise did not cause any marked or consistent change in central venous pressure, in contrast to the substantial contraction of superficial segments which it usually produced. Cold

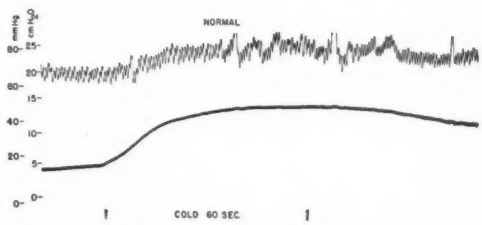


FIG. 5. Effect on central venous and arm segment pressures of immersing both feet and the opposite hand of a normal subject in ice water for 60 seconds. Central venous pressure, in cm. water, appears in the upper tracing and segment pressure, in mm. Hg, in the lower tracing.

was also without effect, except in one case where both feet and one hand were immersed in ice water. This caused an increase of 5 cm. water in central venous pressure and an increase of over 30 mm. Hg in segment pressure (fig. 5). The effect of hyperventilation on central venous pressure was quite variable. In a few cases the central venous pressure was considerably increased after 60 seconds of hyperventilation.

Elevation of the central venous pressure in response to a stimulus which causes superficial veins to constrict suggests that venoconstriction has been widespread enough to cause the overall rise in pressure. The amount of increase in central venous pressure would then constitute some measure of general venoconstrictor activity. However, the present data allow an additional possibility. The central venous pressure was consistently increased after the Valsalva maneuver and tilting, but only occasionally by the other stimuli. Tilting and the Valsalva maneuver tend temporarily to shift blood from the pulmonary to the systemic circulation. Conceivably, readjustment of the blood volume after completion of the Valsalva or tilt might require a minute or more. During this time the systemic blood volume would be increased and the central venous pressure might be raised on this account without any venomotor activity. It would require the transfer of a considerable volume of blood to account for the elevation of central venous pressure by this means alone. The mean rise in central venous pressure after the Valsalva was 3.4 cm. water. In the normal relaxed subject a similar pressure rise results from the infusion of approximately 500 ml. of whole blood.[7] The loss of a large volume of blood from the pulmonary circulation might be expected to cause a drop in pulmonary vascular pressures, if the pulmonary vessels did not constrict greatly. In fact, however, there is a rise in pulmonary vascular pressures. Figure 6 shows the change in pulmonary artery and wedge pressures in normal subjects after the Valsalva maneuver. It is evident that there is an overall increase in both artery and wedge pressures above the pre-Valsalva control level. Pressures were usually highest within the

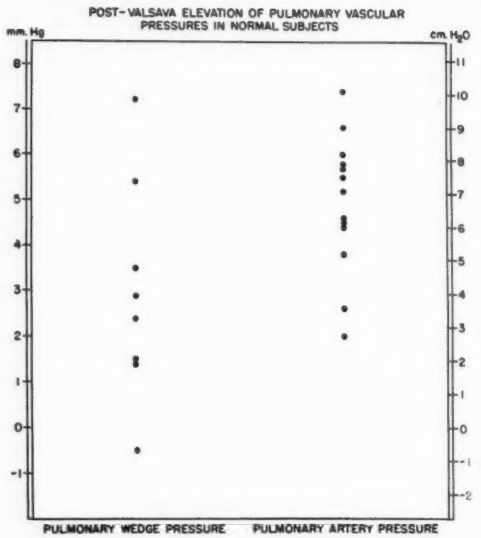


FIG. 6. Change in pulmonary wedge and pulmonary artery pressures of normal subjects after the Valsalva maneuver. The change is measured as post-Valsalva pressure minus resting control pressure. Wedge pressure changes were measured two or three times each in three normal subjects. Pulmonary artery pressure changes were measured in these three subjects and in three additional normal subjects. Mean pressures were measured, usually over two respiratory cycles, and the difference between the highest post-Valsalva pressure and the control pressure is recorded in the figure.

first 20 seconds after release of the Valsalva but a definite elevation was, in general, still evident at 60 seconds. As in the central venous pressure measurements, there was much variability in the amount of pressure change and in some trials there was virtually no pressure change at all. Pulmonary artery and wedge pressures changed by about the same amount, so that there was little change in pressure gradient across the pulmonary circulation. From the rise in pulmonary vascular pressures it is apparent that substantial amounts of blood could not have been transferred from the pulmonary circulation without an extensive pulmonary vasoconstriction. This seems unlikely since the pulmonary pressure gradient remains low and the cardiac output is known not to be greatly reduced in the post-Valsalva period.[8] It appears more probable that the elevation in pulmonary wedge pressure occur

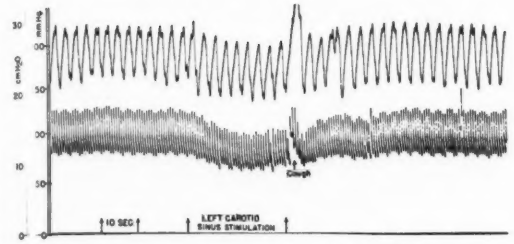


FIG. 7. Simultaneous changes in central venous pressure (upper tracing) and brachial artery pressures resulting from carotid sinus stimulation in a subject with an active vasodepressor response. Heart rate changes very little.

because of a transfer to the pulmonary circulation of blood made available by systemic venoconstriction. Constriction of the superficial veins occurs as has already been demonstrated. In summary, the present data indicate that the post-Valsalva increase in central venous pressure depends upon an active vasoconstriction which involves at least part of the systemic venous system and which may or may not involve the pulmonary circulation as well.

In connection with the use of changes in central venous pressure as an index of venomotor activity, the experiment recorded in figure 7 is of interest. This appears to show a reflex venomotor response in association with an arterial reflex. The subject, a man of 62, had a sensitive vasodepressor response to carotid sinus stimulation and had had frequent episodes of posttussive syncope. As shown in figure 7, stimulation of the carotid sinus caused simultaneous falls in arterial and central venous pressure with little change in heart rate, and the two pressures then recovered simultaneously.

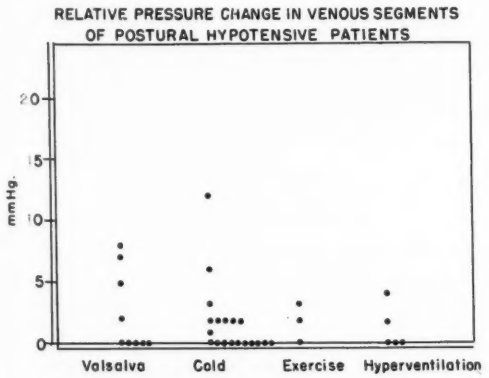


FIG. 8. Pressure response to various stimuli of superficial vein segments of six patients with postural hypotension. Group means are given in table 3.

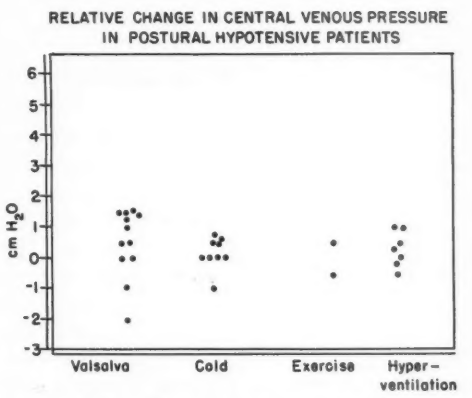


FIG. 9. The effect on central venous pressure of various stimuli applied to six patients with postural hypotension.

Vein Segment and Central Venous Pressure Responses in Postural Hypotension

Observations were made on six patients who had postural hypotension associated with abnormalities of the autonomic nervous system. All were males. One (age 51) had had a sympathectomy (bilateral, T-1 to L-1) four months earlier for arterial hypertension. One (age 69) had idiopathic postural hypotension, and four (ages 36, 41, 48 and 49) had diabetes mellitus.

Measurements were made of the vein segment and central venous pressure responses of these patients to the same stimuli used in the normal subjects except that tilting was omitted because of technical difficulties. The results

TABLE 3.—*Arm Segment Responses in Postural Hypotensives*

	No. of Observations	No. of Subjects	Mean Pressure Increase (mm. Hg)*	Standard Deviation
Valsalva	9	5	2.2	±3.3
Cold	19	6	1.8	±2.1
Exercise	3	3	1.7	±1.6
Hyperventilation	5	5	1.2	±1.8

* Mean of each individual's average response. Segment responses are significantly less than normal ($p < .01$).

are presented in figures 7 and 8 and in table 3. It is apparent that these subjects show very little response of either the superficial segment or the central venous pressure. In the sympathectomized patient and the patient with idiopathic autonomic disease, performance of the Valsalva maneuver caused a very marked drop in blood pressure with momentary loss of consciousness. The other patients also performed the maneuver vigorously, so that the stimulus was at least as severe as in normal subjects. That the veins of such patients still have the ability to contract was demonstrated in the patient with idiopathic autonomic disease. Injection of minute amounts of Neo-Synephrine and epinephrine into the vein segment caused contractions of 30 and 33 mm. Hg.

Discussion

It is believed that the increase in central venous pressure of normal subjects after tilting and the Valsalva maneuver reflects an overall increase in peripheral venous tone. Similar increases in central venous pressure have been found to occur in normal subjects after exposure to positive acceleration on the human centrifuge.[9] With forceful constriction of the superficial veins, blood is shifted to more distensible portions of the venous system. The easily distensible part probably includes the larger central veins, which Donegan[2] found to be noncontractile in experimental animals. Shifting blood into the distensible veins causes a general venous pressure rise which is related to the volume of blood shifted and to the elasticity of the system. The general pressure rise is here measured as an increase in central venous pressure. In a similar way, the central venous pressure, and probably the central venous volume, are increased by increasing the general blood volume with infusions, and are lowered by decreasing the volume with venesection or venous tourniquets.[7, 10, 11] The increase in central venous pressure which results from infusions also depends upon the proportion in which the additional blood is divided between systemic and pulmonary circulations. Only that volume which remains on the systemic side is effective in directly raising the central venous pressure. In normal subjects additions to the general blood volume are distributed to both circulations, with a roughly equal increase in venous pressure on each side.[1] The present finding that central venous and pulmonary capillary pressure are both elevated after the Valsalva maneuver suggests that the extra blood made available by peripheral constriction may also be distributed to both circulations. The present data, however, leave open the possibility that pulmonary vasoconstriction may also be present in the post-Valsalva period. A similar, though larger, elevation of venous pressure in each circulation can be produced by norepinephrine without increase in the pulmonary pressure gradient, presumably through peripheral venous constriction. With the Valsalva maneuver, the venous segment constriction has a reflex basis, since it occurs despite isolation of the arm by an arterial cuff. It is, however, possible that small amounts of norepinephrine may be released and may also play some part in the elevation of central venous pressure. In summary the present data are consistent with the view that the Valsalva maneuver evokes a vigorous reflex peripheral venoconstriction, and that this shifts blood into the central venous region, causing an increase in central venous pressure. The increase in pulmonary wedge pressure may result from an increase in pulmonary blood volume or from pulmonary vasoconstriction. The increase in central venous pressure after tilting appears to be on the same basis.

Tilting and the Valsalva maneuver tend to reduce venous return to the heart and to lower the cardiac output. The resultant drop in blood pressure is partially or completely corrected by widespread arteriolar constriction, with an increase in peripheral arterial resistance. At the same time widespread peripheral venous constriction has the effect of shifting blood centrally and making it available to the heart for the maintenance of output. For sustaining arterial blood pressure under these and similar conditions, arterial and venous constriction are both important, the former for increasing resistance, the latter for maintaining cardiac output.

It has previously been suggested that reflex peripheral venous constriction normally occurs on assuming the upright position and that loss of this reflex in orthostatic hypotension could be responsible for the very large postural drops in cardiac output which may occur in severe cases of the disorder.[14] This view is supported by data obtained from the present patients with orthostatic hypotension. They showed marked impairment or absence of reflex contraction of venous segments, and there was little or no increase in central venous pressure after the Valsalva maneuver. This loss of venous tone can be a significant contributory factor in the production of orthostatic hypotension. When the venous pressure of such patients is raised by increasing the blood volume, cardiac output and arterial pressure are much better maintained in the upright position.[14] It should be pointed out that the basic defect in classical orthostatic hypotension is loss of the ability to achieve adequate arteriolar constriction in response to a drop in pressure. When arteriolar constriction is adequate, large drops in cardiac output can be sustained without a significant drop in mean arterial pressure.

Hyperventilation, exercise, and cold cause superficial segment contraction but do not usually increase the central venous pressure. Hyperventilation is known to have different effects on the blood vessels of different body regions. It reduces blood flow to the skin and brain, but increases flow in the muscles, with an overall reduction in arterial resistance.[15] It is not surprising that superficial venous segment contraction can occur during hyperventilation without sufficient overall contraction to elevate the central pressure. The same considerations apply to the superficial venoconstriction produced by exercise and cold.

When the central venous pressure is increased after the Valsalva maneuver or tilting, the change outlasts contraction in peripheral segments. In experimental animals the splanchnic veins have been found to be more muscular and contractile than the superficial veins. It is possible that the central venous pressure may still be partially maintained by splanchnic venoconstriction after the peripheral system has relaxed.

Summary and Conclusions

1. Reflex venomotor activity in normal subjects has been observed and quantitated by measuring pressures developed within isolated segments of arm and leg veins in response to various stimuli. Vigorous contraction of these segments is produced by the Valsalva maneuver, tilting, exercise, cold, and hyperventilation.

2. The central venous pressure (CVP) of normal subjects is substantially increased for a short time after completion of the Valsalva maneuver and after return from a foot-down tilt to the horizontal position. The response to cold, hyperventilation and exercise is variable but usually very slight. Since pulmonary vascular pressures are also elevated after the Valsalva maneuver, it is suggested that the peripheral venoconstriction induced by the Valsalva is widespread enough to shift considerable extra blood into the central venous and pulmonary regions after thoracic straining is relaxed. It is also possible that pulmonary vasoconstriction may be associated with peripheral constriction. The elevation in central venous pressure is an index of widespread venoconstriction. The increase in central venous pressure after tilting suggests that widespread venoconstriction is a normal postural response. Failure of the central venous pressure to rise after other stimuli which cause vigorous superficial segment constriction suggests that the constrictor effect of these stimuli is limited to a relatively small portion of the venous system.

3. Subjects with postural hypotension show very little increase in segment or central venous pressures in response to stimuli which produce large effects in normal subjects. This loss of reflex venoconstriction contributes to the postural disability of these patients.

Summario in Interlingua

Le activitate venomotor reflexe in subjectos normal esseva observate e mesurate per medio del pressiones disveloppate intra segmentos isolate de venas superficial. Forte contractiones es causate per le experimento de Valsalva, per inclinar le corpore del subjecto, per exponer lo a reducite temperaturas, e per hyperventi-

lation e exercitios. Post le experimento de Valsalva e post inclinar le corpore del subjecto il ha un breve elevation del pression venose central. Le pressiones vascular pulmonar es etiam augmentate post le experimento de Valsalva. Isto pote esser interpretate como indicio de extense venoconstriction con displaciamento central de sanguine. In individuos con hypotension postural le stimulos mentionate provoca pauc o nulle reactiones del pression venose segmental o central. Isto indica un defectuose activitate venomotor reflexe.

REFERENCES

[1] FRANKLIN, K. J.: A monograph on veins. Charles C Thomas, Springfield, 1937.

[2] DONEGAN, J. F.: The physiology of the veins. J. Physiol., **55:** 226, 1926.

[3] CAPPS, R. B.: A method for measuring tone and reflex constriction of the capillaries, venules, and veins of the human hand with the result in normal and diseased states. J. Clin. Invest., **15:** 229, 1936.

[4] LANDIS, E. M. AND HORTENSTINE, J. C.: Functional significance of venous blood pressure. Physiol. Rev., **30:** 1, 1950.

[5] DUGGAN, J. L., LOVE, V. L. AND LYONS, R. H.: A study of reflex venomotor reactions in man. Circulation, **7:** 869, 1953.

[6] GAUER, O. H., SIEKER, H. O., AND HENRY, J. P.: Recording of central venous pressure from the right antecubital vein during small changes in blood volume. Federation Proc., **12:** 1, 1953.

[7] GAUER, O. H.: Venomotor tone and blood volume control. Minnesota Med., **37:** 16, 1954.

[8] MCINTOSH, H. D., BURNUM, J. F., HICKAM, J. B., AND WARREN, J. V.: Circulatory changes produced by the Valsalva maneuver in normal subjects, patients with mitral stenosis, and autonomic nervous system alterations. Circulation, **9:** 511, 1954.

[9] SIEKER, H. O., MARTIN, E. E., GAUER, O. H., AND HENRY, J. P.: A comparative study of two experimental pneumatic anti-G suits and the standard USAF G-4A anti-G suit. WADC Technical Report 52-317, Wright Air Development Center, February 1953.

[10] WARREN, J. V., BRANNON, E. S., STEAD, E. A., JR., AND MERRILL, A. J.: The effect of venesection and the pooling of blood in the extremities on the atrial pressure and cardiac output in normal subjects with observations on acute circulatory collapse in three instances. J. Clin. Invest., **24:** 337, 1945.

[11] STEAD, E. A., JR., BRANNON, E. S., MERRILL, A. J., AND WARREN, J. V.: Concentrated human albumin in the treatment of shock. Arch. Int. Med., **77:** 564, 1946.

[12] DOYLE, J. T., WILSON, J. S., ESTES, E. H., AND WARREN, J. V.: The effect of intravenous infusions of physiologic saline solution on the pulmonary arterial and pulmonary capillary pressure in man. J. Clin. Investigation, **30:** 345, 1951.

[13] FOWLER, N. O., WESTCOTT, R. N., SCOTT, R. C. AND MCGUIRE, J.: The effect of nor-epinephrine upon pulmonary arteriolar resistance in man. J. Clin. Investigation, **30:** 517, 1951.

[14] HICKAM, J. B. AND PRYOR, W. W.: Cardiac output in postural hypotension. J. Clin. Investigation, **30:** 401, 1951.

[15] BURNUM, J. F., HICKAM, J. B. AND MCINTOSH, H. D.: The effect of hypocapnia on arterial blood pressure. Circulation, **9:** 89, 1954.

The Effects of Intravenous Hexamethonium on Venous Pressure of Normotensive and Hypertensive Patients with and without Congestive Heart Failure

By ROBERT R. BURCH, M.D.

The response of atrial pressure, venous pressure, pulse and respiratory rates to intravenous hexamethonium in 38 selected patients was studied. The drug seemed more effective where vascular tone was greater. Increased venous tone was indicated in congestive heart failure. The possible useful role of intravenous hexamethonium as an adjunct in the treatment of congestive heart failure was concluded from the objective and subjective observations made.

THE immediate effects of hexamethonium on venous pressure and congestive heart failure have been reported previously.[1, 2] There was a variable decline in venous pressure associated with some relief of dyspnea. Since the drug seemed to have possible therapeutic value in congestive heart failure, knowledge of the duration of action as well as the time course relationship of changes in venous pressure to arterial pressure, pulse rate and respiratory rate may be important. Since previous observations have been concerned principally with hypertensive heart disease with congestive heart failure, data on the response of patients with normal arterial pressure and elevated venous pressure are lacking.

METHOD

Thirty-eight patients grouped into four categories of study were hospitalized at the Charity Hospital and had been at bed rest for varying lengths of time before these observations were made. Ten of the subjects who were convalescing from various disease states were normotensive without congestive heart failure (table 1), nine were normotensive patients with congestive heart failure (table 2), 10 were hypertensive patients without congestive heart failure (table 3), and nine had hypertensive heart disease and congestive heart failure (table 4). In addition to bed rest, all of the patients with congestive heart failure were receiving therapy including digitalis, salt restriction, diuretics and, in some cases, nasal oxygen at the time of the study.

Venous pressure was measured in the median basilic vein by means of a saline manometer and all values were corrected to the phlebostatic level.[3] All observations included measurements of venous pressure, arterial pressure, pulse and respiratory rates as well as the usual clinical observations including attention to gallop rhythm, pulsus alternans, basal rales and dyspnea. Several consecutive observations were made to establish a control or basal level and were repeated as often as possible during intravenous injection of hexamethonium and at hourly intervals thereafter until the venous pressure returned to the control level. Prior to, immediately following the injection of hexamethonium, and at the end of the observation, the magnitude of the hepatojugular reflux was recorded after pressure had been exerted on the right upper quadrant of the abdomen for one minute.

The rate of injection as well as the dosage administered was recorded. There was considerable variation in the dosage and the rate of administration, the latter being intermittent (tables 1–4, figs. 1–4).

RESULTS

The results are summarized for all four groups separately in tables 1 through 4 and figures 1 through 4.

In Normotensive Subjects without Congestive Heart Failure. In patients in this category as well as in those in the other three categories, there were essentially two types of responses to the intravenous injection of hexamethonium (table 1 and fig. 1). The response in 8 of the 10 subjects in this group (fig. 1*a* and table 1,

Aided by a United States Public Health Service Research Grant (H143).

From the Department of Medicine, Tulane University School of Medicine and Charity Hospital of Louisiana at New Orleans.

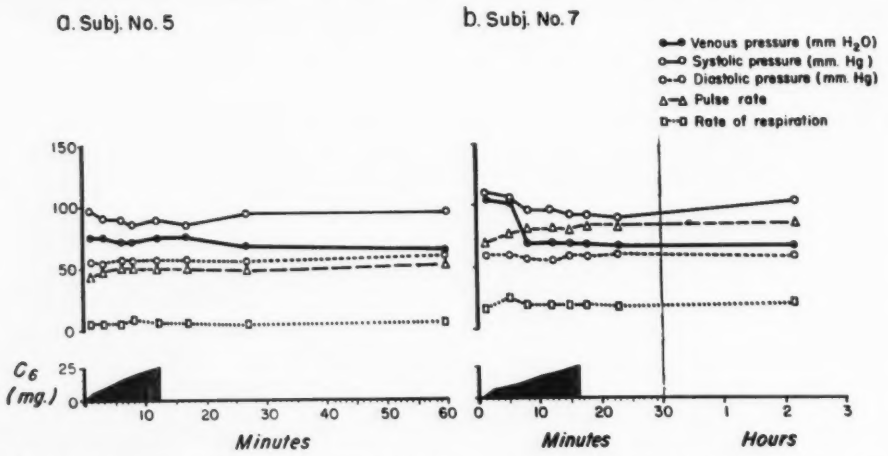


FIG. 1. Effects of intravenous hexamethonium in control subjects. (*a* and *b*) The blood pressure, venous pressure, pulse and respiratory rate in two control subjects, illustrating the two types of responses encountered in this group. The amount and rate of injection of hexamethonium is indicated.

TABLE 1.—*Summary of the Clinical Data and Responses to Intravenous Injection of Hexamethonium in Ten Control Patients. All Patients Were Afebrile and Convalescent when Studied*

Subject No.	Clinical state	Age (Yrs.)	Dose given (mg.)	Time for injection (min.)	Venous Pressure (mm. H_2O)					Bl. P. (mm. Hg)			
					Control		Immediately postinjection		Time for return to control level in hours	Control	Change	Change in pulse	Change in respiration
					Resting	Hepatojugular reflux	Resting	Hepatojugular reflux					
1	Pneumonia	50	12.5	29	155	0	170	0	—	110/75	−22/12	−8	0
2	Rheumatoid arthritis	44	25.0	27	135	0	110	0	—	116/78	−16/4	0	0
3	Acute gastritis	31	10.0	4	84	0	80	0	—	112/90	−28/20	+10	0
4	Endemic typhus	49	25.0	14	60	0	49	0	—	120/80	−15/5	+8	0
5	Psychoneurosis	64	25.0	11	88	0	80	0	—	115/70	−25/16	+12	0
6	Psychoneurosis	46	25.0	14	128	0	126	0	—	140/84	−20/0	+8	0
7	Acute pyelonephritis	27	25.0	14	108	0	65	0	2.5+	110/60	−20/0	+16	0
8	Diabetes mellitus Rheumatoid arthritis	44	25.0	13	82	0	78	0	—	140/90	−20/14	0	0
9	Infectious hepatitis	39	25.0	13	92	0	102	0	—	145/85	−20/5	+14	0
10	Infectious hepatitis	21	25.0	15	110	0	108	0	—	140/82	+15/18	+14	0
Mean			22.3	15.4	104	0	97.8	0	—	125/79	−16.6/6.8	+7.4	0

subject 5) was characterized by no significant change in venous pressure, arterial pressure, or pulse and respiratory rates. In two patients there was a decline in venous pressure and essentially no change in arterial blood pressure (fig. 1).

The average dose of hexamethonium was 22.3 mg. administered in an average of 15.4 minutes. Venous pressure declined 6.2 mm. H_2O, arterial pressure declined 16.6/6.8 mm. Hg and pulse rate increased 7.4 per minute. There was no change in respiratory rate.

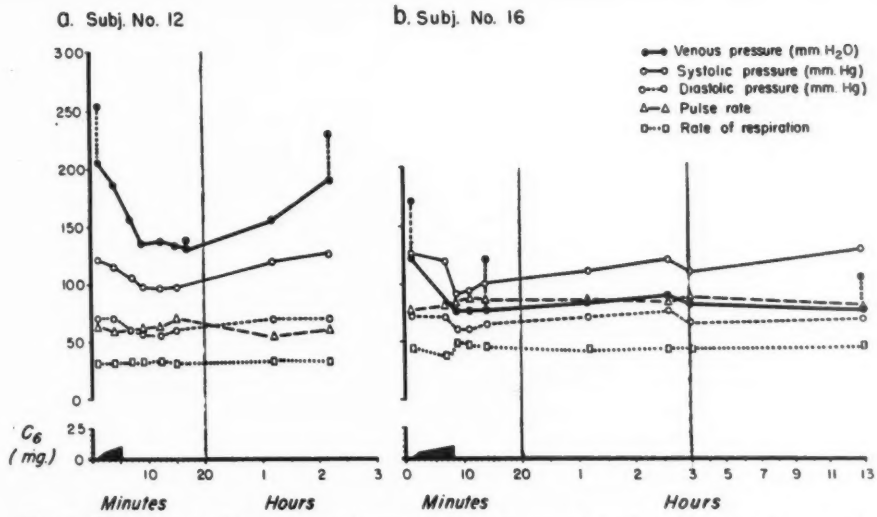


FIG. 2. The effects of intravenous hexamethonium in normotensive subjects with congestive heart failure. (*a* and *b*) The blood pressure, venous pressure, pulse and respiratory rate in two normotensive subjects with congestive heart failure, illustrating the two types of responses encountered in this group. The amount and rate of injection of hexamethonium is indicated. The dotted lines indicate the magnitude of the hepatojugular reflux.

TABLE 2.—*Summary of the Clinical Data and Responses to Intravenous Injection of Hexamethonium in Nine Normotensive Patients with Congestive Heart Failure*

Subject No.	Clinical state	Age (Yrs.)	Dose given (mg.)	Time for injection (min.)	Venous Pressure (mm. H_2O)					Bl. P.		(mm. Hg)	
					Control		Immediately postinjection		Time for return to control level in hours	Control	Change	Change in pulse	Change in respiration
					Resting	Hepatojugular reflux	Resting	Hepatojugular reflux					
11	RHD	43	10.0	17	225	35	146	34	2.5	130/86	−48/34	+4	−6
12	ASHD, Diabetes mellitus, bronchopneumonia	53	10.0	3	205	50	133	4	2	124/70	−28/12	0	0
13	RHD, bronchopneumonia	47	10.0	5	275	67	185	13.5	1	140/85	−60/33	0	0
14	Heart disease unknown etiology	49	7.5	6	340	110	240	110	4	140/94	−44/24	+18	+10
15	HCVD*	44	3.75	8	285	125	135	—	3	154/90	−34/10	−12	−4
16	ASHD	51	10.0	6	126	46	74	46	13+	122/70	−30/10	+16	0
17	Syph. HD	66	5.0	1	170	60	88	10	3+	144/70	−44/22	−28	0
18	ASHD	51	25.0	16	112	40	112	0	0	115/70	−21/2	0	0
19	Syph. HD	74	10.0	7	300	56	215	—	—	130/58	−32/8	+6	−4
	Mean		10.1	7.7	226	65	147	48	4.0	133/78	−38/17	0	0

HD, rheumatic heart disease; ASHD, arteriosclerotic heart disease; Syph. HD, syphilitic heart disease; HCVD, hypertensive cardiovascular disease.

Subject 15 had sustained hypertension previously, but at the time of this study the blood pressure was normal.

In Normotensive Patients with Congestive Heart Failure. The response of four normotensive patients with congestive heart failure followed the pattern summarized by figure 2*a* and table 2, subject 12. There was a more marked and rapid fall in venous pressure than in arterial pressure with the pulse and respiratory rates remaining unchanged. With the fall in

venous pressure, the hepatojugular reflux was absent but returned when the venous pressure approached control level again. Both arterial pressure and venous pressure returned to the control levels within two hours. The other type of response summarized by figure 2*b* and table 2, subject 16, was observed in 4 patients. Here again, venous pressure began to fall before arterial pressure. The magnitude of the hepatojugular reflux was not diminished by the injection, and at the end of a 13-hour period arterial pressure had returned to the control level while venous pressure had failed to do so.

The average dose of hexamethonium was 10.1 mg. injected over a period of 7.7 minutes. Following intravenous administration of hexamethonium, there was a mean fall in venous pressure of 79 mm. H_2O and a decrease in the magnitude of the hepatojugular reflux of 17 mm. H_2O. The venous pressure returned to control levels in an average of 4.0 hours. The arterial pressure declined 38/17 mm. Hg and returned to control level sooner in some patients than did the venous pressure. There were no consistent changes in the pulse or respiratory rates.

In Hypertensive Patients without Congestive Heart Failure. The response of 10 patients in the hypertensive group without congestive heart failure is summarized by figure 3. Six patients presented the pattern shown in figure 3*a* and

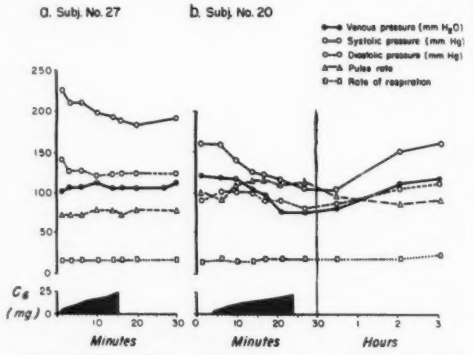


FIG. 3. The effects of intravenous hexamethonium in hypertensive subjects without congestive heart failure. (*a* and *b*) The blood pressure, venous pressure, pulse and respiratory rate in two hypertensive subjects without congestive heart failure, illustrating the two types of responses encountered in this group. The amount and rate of injection of hexamethonium is indicated.

table 3, subject 27, which consisted of a fall in arterial pressure with essentially no change in venous pressure or pulse and respiratory rates following the injection of hexamethonium. The other four patients of this group had a moderate simultaneous decline in arterial pressure and venous pressure with a return to control levels within two hours (fig. 3*b* and table 3, subject 20). Pulse or respiratory rates did not change.

The average dose of hexamethonium was

TABLE 3.—*Summary of the Clinical Data and Responses to Intravenous Injection of Hexamethonium in Ten Hypertensive Patients without Congestive Heart Failure*

Subject No.	Clinical state	Age (Yrs.)	Dose given (mg.)	Time for injection (min.)	Venous Pressure (mm. H_2O)					Bl. P. (mm. Hg)			
					Control		Immediately postinjection		Time for return to control level in hours	Control	Change	Change in pulse	Change in respiration
					Resting	Hepatojugular reflux	Resting	Hepatojugular reflux					
20	Essent. hypertens.	53	25.0	20	122	0	76	0	2	180/110	−58/20	+8	0
21	Essent. hypertens.	46	15.0	12	104	0	80	0	1+	250/150	−100/52	+22	0
22	Essent. hypertens.	49	12.5	16	89	0	91	0	—	208/138	−50/8	+20	0
23	Essent. hypertens.	34	25.0	17	104	0	70	0	4+	182/132	−60/32	+4	0
24	Essent. hypertens.	22	25.0	12	117	0	115	0	—	160/105	−20/10	0	0
25	Essent. hypertens.	53	25.0	24	55	0	51	0	—	170/110	−30/15	+4	0
26	Malig. hypertens.	48	25.0	14	95	0	76	0	—	230/150	−32/20	+8	0
27	Essent. hypertens.	40	25.0	14	100	0	105	0	—	225/140	−43/18	+4	0
28	Essent. hypertens.	37	25.0	11	156	+9	132	0	—	244/142	−30/0	0	0
29	Essent. hypertens.	14	25.0	13	125	0	132	0	—	210/150	−40/12	+4	0
Mean			22.8	15.3	107	0.9	93	0	+0.7	206/134	−47/19	+6.6	0

2?.8 mg. administered over a period of 15.3 minutes. Venous pressure declined an average of 14 mm. H_2O and arterial pressure declined an average of 47/19 mm. Hg. There was a slight increase in pulse rate of 6.6 per minute without a change in respiratory rate.

In Patients with Hypertensive Heart Disease with Congestive Heart Failure. Four of the nine patients with hypertensive heart disease and congestive heart failure responded with marked simultaneous fall in venous pressure, arterial pressure and pulse rate, with little change in respiratory rate (fig. 4*a* and table 4, subject 35). The hepatojugular reflux was absent following hexamethonium. At the end of a three-hour period, the venous pressure and the magnitude of the hepatojugular reflux had returned to the control level, but the arterial pressure and pulse rate remained at a lower level. The other type of response elicited in the other five patients is summarized by figure 4*b* and table 4, subject 38. Following administration of the drug there was also a marked fall in venous pressure and arterial pressure but no change in the magnitude of the hepatojugular reflux or pulse and respiratory rates. Venous pressure required over eight hours to return to control levels while the blood pressure had not returned to control levels in 20 hours.

The average dose of hexamethonium was 21 mg., injected over a period of 11 minutes. The decline in venous pressure averaged 85 mm. H_2O and the hepatojugular reflux decreased 18 mm. H_2O. The average time for the venous pressure to return to the control level was 3.5 hours. Arterial pressure declined an average of 44/26 mm. Hg and pulse rate was reduced 13.5 beats per minute. The respiratory rate changed insignificantly.

The Effects of Intravenous Administration of Hexamethonium on Dyspnea, Basal Rales, Pulsus Alternans, and Gallop Rhythm. Two of the nine normotensive subjects with congestive heart failure with a protodiastolic gallop rhythm had no change in the rhythm following injection of the drug. All nine subjects were dyspneic prior to injection, and all experienced considerable improvement in this symptom.

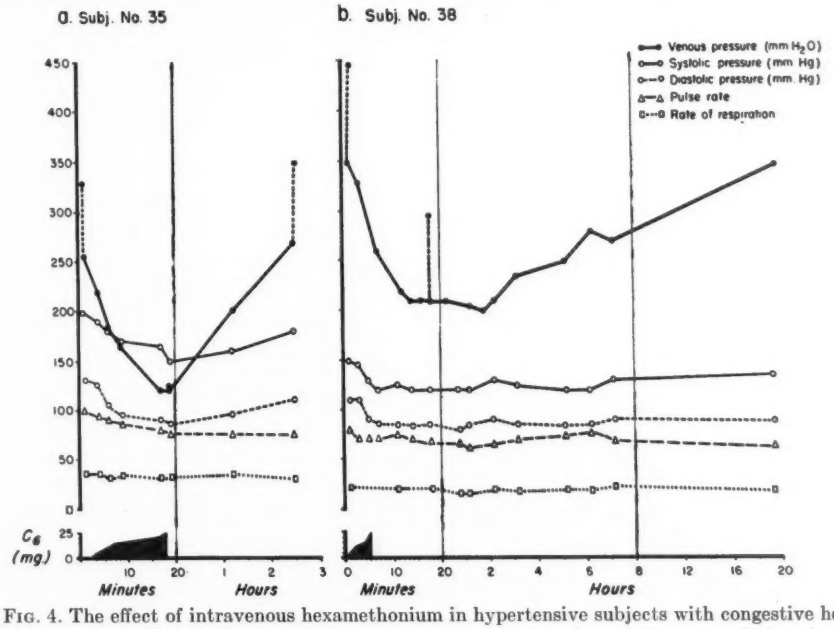


FIG. 4. The effect of intravenous hexamethonium in hypertensive subjects with congestive heart failure. (*a* and *b*) The blood pressure, venous pressure, pulse and respiratory rate in two hypertensive subjects with congestive heart failure, illustrating the two types of responses encountered in this group. The amount and rate of injection of hexamethonium is indicated. The dotted lines indicate the magnitude of the hepatojugular reflux.

TABLE 4.—*Summary of the Clinical Data and Responses to Intravenous Injection of Hexamethonium in Nine Patients with Hypertensive Heart Disease and Congestive Heart Failure*

Subject No.	Clinical state	Age (Yrs.)	Dose given (mg.)	Time for injection (min.)	Venous Pressure (mm. H_2O)					Bl. P. (mm. Hg)			
					Control		Immediately postinjection		Time for return to control level in hours	Control	Change	Change in pulse	Change in respiration
					Resting	Hepatojugular reflux	Resting	Hepatojugular reflux					
30	HCVD	29	25.0	14	138	+28	78	20	4.5	255/160	−55/20	−16	−4
31	HCVD*	41	25.0	15	105	0	35	0	—	250/160	−40/5	0	0
32	HCVD, Diabetes mellitus	67	5.0	6	210	+60	135	—	2	210/110	−40/30	0	0
33	HCVD, Ac. Pulmon. edema	40	25.0	16	268	+52	180	20	4+	296/180	−74/40	−32	−14
34	HCVD	52	25.0	13	208	+52	146	40	3	170/120	−24/12	0	0
35	HCVD, Ac. pulmon. edema	52	25.0	15	252	+88	120	0	3	200/130	−50/50	−20	−4
36	HCVD	47	25.0	13	350	+140	260	170	2	122/108	−24/18	−42	0
37	HCVD, Ac. pulmon. edema	65	10.0	5	148	+44	106	16	2	180/105	−62/30	−4	0
38	HCVD	44	25.0	4	360	+90	210	84	7	150/110	−25/25	−8	0
Mean			21.0	11	226	62	141	44	3.5	204/130	−44/26	−13.5	−2

* Patient had pulsus alternans and gallop rhythm.

However, there was no dramatic objective change in respiration.

Among the nine patients with hypertensive heart disease with congestive heart failure, four had pulsus alternans. The sign disappeared in two patients following administration of the drug, lessened in degree in one patient, and remained unchanged in the other patient. There were seven instances of protodiastolic gallop rhythm in this group. In three instances the rhythm disappeared following administration of the drug, and it was unaffected in the remaining four patients. Dyspnea was present in seven of the nine patients in this group prior to use of the drug. In the three patients (subjects 33, 35, 37) who had acute pulmonary edema, there was a dramatic decrease in dyspnea following the injection of hexamethonium. They were able to dispense with the use of oxygen shortly after administration of the drug. The remaining four patients who had dyspnea prior to the injections reported considerable improvement in this symptom. Those subjects in both the normotensive and hypertensive groups who reported relief of dyspnea had little change in respiratory rate, yet they appeared more comfortable and respiration was obviously accomplished with less effort.

DISCUSSION

It should be emphasized that the patients were grouped solely on the basis of hypertension and congestive failure. In the two groups of patients with failure, normotensive and hypertensive, there was considerable variation in the clinical state of the failure. The subjects had already received varying periods of bed rest and varying amounts of drugs before this study was conducted. Some of the patients were improving in their state of failure, others were apparently stable and others were progressively becoming worse. Since the state of the congestive heart failure influences electrolyte metabolism, extent of edema fluid, body weight and the initial venous pressure, it would be expected to have an effect on the results observed in these experiments. In fact, many of the discrepancies among observations on congestive heart failure reported in the past may have been due to a failure or inability to define precisely the state of the failure.

The total dose of hexamethonium administered as well as the time required for injection varied in these experiments. The drug was administered slowly to permit adequate observation of its effects. When definite effects were noted, administration of the drug was

s opped regardless of the dose administered up to that point. The maximum dose administered, regardless of the degree of response, was 25 mg. Thus, the dosage varied considerably and in a relatively unstandardized manner. It is also apparent that doses larger than 25 mg. might have increased the magnitude of the response or might have caused a response when none was observed with the maximum dose of 25 mg. used in these studies. It is interesting to note that the average dose of hexamethonium was about the same for all the subjects without failure and for the hypertensive group with failure. The average dose required to elicit a response in the patients with congestive heart failure and normal arterial pressure was approximately half that of the other groups. Only one patient in this group received as much as 25 mg. and one patient had a marked response to as little as 3.75 mg. The reason for this "increased sensitivity" in the normotensive subjects with congestive heart failure is not apparent. This type of reaction had been observed by others using hexamethonium and other vasodilating agents.[1, 4, 5]

It is generally agreed that drugs and procedures which influence peripheral blood vessels exert the same influence on both the arteries and the veins.[6] However, it was possible to select the patients in these experiments so that the effects of the drug could be observed when both arterial and venous pressure (tone) were normal, when the venous pressure was high and arterial pressure normal, when arterial pressure was high and venous pressure normal and when the pressures were elevated in both the arterial and venous sides of the circulation. By such a selection, it was possible to observe the effects of hexamethonium on the reactions of arteries and veins when either or both showed a disproportional increase in tone. In subjects who had normal arterial and venous pressures—therefore normal tone—(group 1), ganglionic blockade was without much effect. However, the degree and duration of its effect on the veins and arteries differed in two instances. In the normotensive subjects who had congestive heart failure with venous hypertension (group 2) the decline in arterial pressure was greater than in the normotensive patients without failure. The decline in venous pressure in the subjects of group 2 was considerably greater than that in patients of group 1 in both absolute values and in percentile levels. The decline in venous pressure in the subjects of group 2 was greater than the decline in arterial pressure which declined only slightly. Thus, although the arterial pressure was within the established limits of normal in these subjects with congestive heart failure, there was evidence of an increase in arteriolar and arterial tone when compared with the subject with normal arterial pressure but without failure.

In hypertensive subjects without heart failure (group 3) the decline in arterial pressure was comparable to the change in pressure in the hypertensive patients with congestive heart failure in both absolute values and percentile levels. However, in subjects of group 3 the decline in venous pressure was much smaller than that in those of group 4 with venous hypertension. It was also observed that the subjects in whom venous pressure was normal, there was relatively little change in venous pressure following hexamethonium, although the arterial pressure declined (group 3).

In all subjects in whom there was an increase in venous pressure, the effect on venous pressure was greater regardless of the state of the associated arterial pressure. It was, therefore, demonstrated that the effect upon the veins was greater when the venous tone was abnormally increased. Furthermore, hexamethonium resulted in different degrees of reaction in the arterial and venous sides of the circulation. Not only did the degree of reaction differ, but there was a variation in the duration of the effect on the venous and arterial pressures as evidenced by the fact that the return to the control level of either was independent of the other. The actual time required for the venous pressure to return to the base-line level varied considerably; in some instances return to this level was not accomplished during the period of observation.

Additional evidence of the action of hexamethonium on venous tone was available from

studies on the hepatojugular reflux. With normal venous tone, venous pressure in the arm responded to right upper quadrant pressure either by no change in pressure or a decrease, whereas when the venous pressure was elevated, the response consisted of a further increase in pressure.[7, 8] The effect of right upper quadrant pressure was noted before and after hexamethonium. In some instances, the absolute rise in venous pressure in the arm after right upper quadrant pressure was as great following hexamethonium but simply reached a lower maximal level. In other instances, this rise in venous pressure was interrupted by the use of hexamethonium. These variations may, in part, be due to the failure to standardize the procedure. However, the results do indicate that hexamethonium exerted a marked effect on the veins when their tone was abnormally increased.

Hexamethonium resulted in an impressive improvement in the clinical status of the patients in failure. All the patients in groups 2 and 4 were subjectively and objectively more comfortable following administration of hexamethonium, a response reported previously.[1, 9, 10] In the few instances in which acute left ventricular failure was present (subjects 33, 35, 37), the clinical improvement was most dramatic. The pulmonary edema and dyspnea rapidly cleared, and there was a disappearance of the protodiastolic gallop rhythm and the pulsus alternans in two subjects. The pulse rate declined an average of 20 beats per minute. In three instances, the gallop rhythm disappeared immediately after injection of the drug. The duration of the effect on venous pressure, determined by the time required to return to the control level, varied from 1 to 13 hours or longer. In no instance was there an untoward reaction to hexamethonium in the dosage used. In some instances the pulse rate increased, in others it decreased and when auricular fibrillation was present there was no change. It was difficult to evaluate the effects of hexamethonium alone on the course of the failure as other therapy was already present.

Summary

These observations showed that hexamethonium lowers venous pressure in congestive heart failure and that the effect on the peripheral arteries, arterioles and veins was greatest where tone was highest. The duration of the effect on venous pressure varied from 1 to 13 hours or longer. These observations also indicate the possible value and role of hexamethonium in the management of congestive heart failure.

Summario in Interlingua

Vinti patientes sin insufficientia myocardiac qui recipeva 22,5 mg hexamethonium per administration intravenose, exhibiva nulle significative cambiamento de pression venose. Le pression arterial decresceva 16/7 mg Hg in normotensivos e 47/19 mg Hg in hypertensivos. Dece patientes normotensive con insufficientia myocardiac, qui recipeva 21 mg hexamethonium, exhibiva un reduction del pression venose de 86 mm H_2O e un reduction del pression arterial de 38/17 mg Hg. In nove patientes hypertensive con insufficientia myocardiac, qui recipeva 21 mg hexamethonium, le pression venose se reduceva per 74 mm H_2O e le pression arterial per 44/26 mm Hg. Le refluxo hepatojugular in le majoritate del patientes con insufficientia myocardiac esseva abolite o reducite post le administration de hexamethonium. Le pression venose e le pression arterial retornava al nivello de controlo le un independente del altere. Omne le patientes con insufficientia myocardiac monstrava meliorationes symptomatic. Le observationes monstrava que le effecto del administration intravenose de hexamethonium esseva le plus grande in le casos in que le tono del vasos sanguinee esseva le plus alte. Le possibile uso de hexamethonium como adjuncto al tractamento de insufficientia myocardiac es indicate.

REFERENCES

[1] Kelly, R. T., Fries, E. D., and Higgins, T. F.: The effects of hexamethonium on certain manifestations of congestive heart failure. Circulation **7:** 169, 1953.

[2] Turner, R.: "Medical sympathectomy" in hypertension. A clinical study of methonium compounds. Lancet **2:** 353, 1950.

[3] BURCH, G. E.: A Primer of Venous Pressure. Philadelphia, Lea & Febiger, 1950.

[4] HAYWARD, G. W.: Tetraethyl ammonium bromide in hypertension and hypertensive heart-failure. Lancet **1:** 18, 1948.

[5] RELMAN, A. S., AND EPSTEIN, F. H.: Effect of tetraethylammonium on venous and arterial pressure in congestive heart failure. Proc. Soc. Exper. Biol. & Med. **70:** 11, 1949.

[6] HOOKER, D. R.: Evidence of the functional activity on the part of the capillaries and venules. Physiol. Rev. **1:** 112, 1921.

[7] BURCH, G. E., AND RAY C. T.: Mechanism of the hepato-jugular reflux test in congestive heart failure. Am. Heart J. In press.

[8] HULTGREN, H. N.: The effect of increased venous return on the venous pressure in patients with congestive heart failure. Am. Heart J. **39:** 592, 1950.

[9] HALMÁGYI, D., FELKAI, B., IVÁNYI, J., AND HETÉNYI, G., JR.: The role of the nervous system in the maintenance of venous hypertension in heart failure. Brit. Heart J. **14:** 101, 1952.

[10] BURCH, G. E.: A method for measuring venous tone in digital veins of intact man; evidence for increased digital venous tone in congestive heart failure. Tr. A. Am. Physicians. In press.

Flow Through Collapsible Tubes: Augmented Flow Produced by Resistance at the Outlet

By SIMON RODBARD, M.D., PH.D.

The physical laws describing the character of flow through blood vessels may depart radically from those which have been developed by engineers and physicists for uniform flow through rigid tubes of uniform diameter. These deviations are marked in the case of flow through collapsible tubes, such as blood vessels and valves. At critically high velocities, the flow pattern may be transformed from a quiet, uniform smooth-flowing stream to an interrupted series of jets with the production of audible sound and with marked energy losses. The present study deals primarily with the "paradoxically" increased flow which may take place through collapsible tubes when a resistance is added to the outlet from the system. This marked deviation from the laws for rigid tubes is attributed to the vessel-distending effects of the added resistance, and to the inhibition of the phenomenon of recurrent collapsibility. The present *in vitro* experiments are used to attempt to explain certain paradoxical findings in flow through the collapsible tube systems of the body.

WHEN flow takes place at critically high velocities through a collapsible vessel, instabilities appear which bring about fragmentation of the stream, vibrations, and marked energy losses.[1] These phenomena result because the distending (lateral) pressure falls at a site of high velocity.* When this pressure drop is of sufficient magnitude, the lateral pressure distending the walls is less than the counterforce; the walls are therefore forced closer together. Consequent to this partial constriction of the tube there is a still greater velocity of the stream in this segment, and there is a further fall in distending pressure; the lumen is thereby further reduced. The process progresses until the tube is almost completely closed. At this point, velocity falls nearly to zero (demonstrated by high speed cinematography), and the entire energy of the stream acts to distend the constricted segment. With reopening of the tube, flow begins again; distending pressure then falls, and the cycle is repeated.

It has been suggested that this process of recurrent closing and opening (flitter) of the tube may be related to the production of murmurs and may explain some of the marked energy losses associated with such vibrations (1). Analysis of the mechanism of flitter suggested that an increased resistance to outflow from a collapsible segment might produce an apparent paradoxical increase in flow. Studies were undertaken to test this thesis.

GENERAL METHODS

A modification of a previously described hydraulic model was used (fig. 1). This consisted of a water column maintained at a fixed level which served to drive water (15 to 20 C) through a short segment (3 cm. long) of soft walled collapsible tubing (surgical Penrose) with a diameter of 6 mm. The fluid then passed through a length of a thick walled rubber tubing of wide lumen into a hanging reservoir set at a given height.

In order to be able to produce graded narrowings of the collapsible segment, it was enclosed in a glass cuff. Air was pumped into the cuff cylinder by

From the Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago, Illinois.

This study was aided by a grant from the National Heart Institute (H690). This department is supported in part by the Michael Reese Research Foundation.

* This effect results from the law of conservation of energy, first expressed by Daniel Bernoulli in 1738 (Hydrodynamica, Sive, de Viribus et Motivibus Fluidorum Commentarii; Argentorati: J. R. Dulsecker). In the present context this holds that the *total energy* of a given volume of fluid remains constant. Thus, a column of fluid at rest with a pressure of 100 cm. of water would express this total energy by distending the walls of the vessel (lateral pressure). If the pressure head were maintained constant, and the fluid were not permitted to move, the distending pressure would now be less because of the diversion of some of the energy to produce movement or velocity. The fall in lateral pressure at any point is an index, under these conditions, of the velocity of the stream at that point.

means of a rubber syringe bulb; cuff pressure was registered with a water manometer.

Flow was registered with a rotameter. The frequency of the flitter process was determined with a stroboscope. When indicated, sounds were recorded with a phonocardiographic apparatus.*

The lateral pressure immediately upstream and downstream to the collapsible segment was measured in some instances. As expected, these values were related to the driving pressure head minus a factor related to the velocity of the stream (flow per unit of cross section area). These data are not given in the present report.

Several types of resistance to outflow from the collapsible tube were utilized. These are described in appropriate sections below.

Results

1. Flow Through a Rigid Tube

For base line studies, the rubber segment was replaced by a brass tube of 6 mm. in diameter and 3 cm. long. As expected flow through this system was dependent essentially on the difference in pressures between the inlet and outlet (fig. 1). At a pressure difference of 130 cm. water, 29 ml. per second was delivered. As the distal (outlet) resistance was raised by increments, flow diminished progressively. At 100 cm. water effective pressure head (inlet minus outlet pressure), 25 ml. was delivered per second; at 50 cm., 13 ml. was delivered. Delivery through this relatively rigid system was greater than any of the flows obtained under comparable pressure conditions with the collapsible penrose tubing.

2. Flow Through a Collapsible Tube

For the following experiments the driving pressure head was set at 100 cm. water above the level of the collapsible segment. The level of outflow was set initially at 30 cm. water below the segment. The cuff surrounding the collapsible tube was open to air, that is, under no compression. Under these conditions the flow through the system was 25 ml. per second (compared to 29 when a rigid tube was used).

As the cuff pressure was raised by increments, the flow fell in an irregular fashion. This effect can be seen by noting the flow at the origin (abscissa) of the various lines in

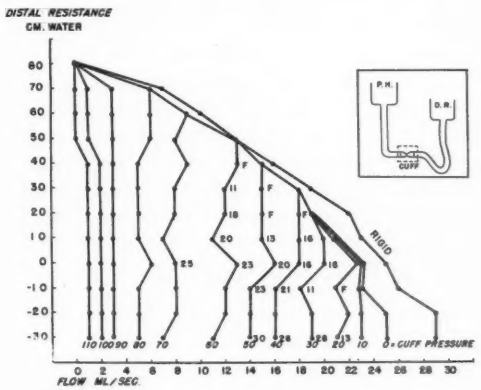


FIG. 1. Inset gives the design of the apparatus used. PH represents the inlet driving *Pressure Head* maintained in a hanging reservoir at a fixed height. Flow passes through a segment of tubing under study, shown as the narrowed portion of the tube. This is surrounded by an enclosed cylinder, labelled "Cuff." In some experiments a rigid brass tube was used in this position. In others, a segment of Penrose tubing was used. The Penrose segment could be "constricted" by increasing the air pressure in the cylinder (cuff pressure). The outlet pressure serving as the distal resistance (DR) in these experiments was maintained constant by means of a second reservoir hanging at a fixed level.

The graph shows the effect of the height of the outflow level on delivery. The inlet pressure head was maintained at 100 cm. above the segment of collapsible tube under study. The vertical axis gives the height of the outlet above or below the collapsible tube, labelled as Distal Resistance. The horizontal axis gives delivery in milliliters per second. The line labelled "Rigid" gives the flow when the collapsible tube was replaced by a segment of copper tubing, and provides a baseline. As the outlet height is raised (vertical axis), flow is reduced progressively as expected. The other 12 lines represent flow through the collapsible tube compressed by cuff pressures in centimeters of water as noted with slanted numerals. As the distal resistance (level of the outlet) is raised, flow may increase, decrease, or remain unchanged, depending on the setting of the cuff pressure. Under some conditions, the walls of the collapsible tube can be seen by means of stroboscopic light to be closing and opening (flitter) at regular rates. The repetition rate of these vibrations is given in the upright numerals accompanying some of the dots. The letter "F" indicates the presence of slow or irregular vibrations of the tube which could not be resolved and counted by stroboscope. Absence of a number at a dot indicates that no vibration was discerned. Discussed in the text.

* Twinbeam Cardiette (Sanborn).

figure 1. For example, at a cuff pressure of 10 cm. water, flow was 23 ml. per second. When the cuff pressure was raised to 20 cm. water, flow fell to 21 ml. per second, and the soft rubber wall was seen by stroboscope to be collapsing recurrently at a rate of 13 times per second. Further increases in cuff pressure caused an irregular but progressive reduction in flow, so that at a cuff pressure of 50 cm. water the flow was only 14 ml. per second; at a cuff pressure of 70, flow was 7 ml. per second and at a cuff pressure of 110, it was only 1 ml. per second.

At the velocities which we studied, delivery is dependent primarily on the viscosity of the fluid and the length and diameter of the pipe system. Since tap water at 15 to 20 C. was used throughout, there were no significant changes in viscosity. The system was arranged so that the length of the various pipes remained unchanged. The only factor which was observed to change in the foregoing experiments was the diameter of the collapsible tube.

In accord with the laws for flow through tubes, the delivery through a system is related to the fourth power of its diameter.* The introduction of pressure into the cuff acts to reduce the diameter of the collapsible tube and in this way can markedly increase the resistance to flow. Very small changes in diameter may produce great increases in resistance, since this is a function of the fourth power of the diameter.

With the onset of recurrent collapsibility the problem is complicated further. Under these conditions the diameter of a portion of the tube is changing rapidly from moment to moment, producing enormous variations in resistance. At high cuff pressures (severe stenosis), flow becomes minimal because of the high resistance to flow through the compressed tube and the flitter phenomenon is suppressed. A seepage flow continues however, even when the cuff pressure is higher than the effective pressure head.

Details of the phenomenon of recurrent collapsibility including energy losses, murmur production, and fragmentation of the stream are given in a previous communication.[1]

3. *The Effect of a Distal Resistance*

An analysis of the mechanism of flitter suggested that under certain circumstances the provision of a resistance to outflow might enhance flow through a collapsible tube. Evidence for this was already available in the work of Holt.[2] This interpretation was based on the fact that a distal resistance would increase the distending pressure acting on the collapsed segment, and thereby partially eliminate the most effective hindrance to flow: the progressive and recurrent narrowing of the collapsible segment.

Outflow or distal resistances were produced by three different means: (a) provision of an outflow column set at various heights; (b) use of graded orifices at the outflow, and (c) use of a second or distal collapsible segment. These had essentially similar effects on delivery.

a. *Distal Resistance Due to Water Column at Outlet.* The effect of the height of the outlet on the delivery was first recorded with the collapsible tube exposed to atmospheric pressure. When the driving head was 100 cm. of water, and the outlet was 30 cm. below the level of the collapsible tube (a total effective head of 130 cm. water), the flow was 25 ml. per second. As the level of the outlet was raised, the delivery fell consistently but irregularly (fig. 1). Thus, with the outlet at the level of the collapsible tube (effective pressure head equals 100 cm. water), flow was 23 ml. per second. Further raising of the outflow level

* The Hagen-Poiseuille formulation is stated mathematically as:

$$Q = \frac{\pi(P_i - P_o)\, d^4}{128 \mu L}$$

where Q is the quantity of fluid delivered, π is the constant 3.14, P_i is the pressure at the inlet, P_o is the pressure at the outlet, d is the diameter of the tube, μ is the viscosity of the fluid and L is the length of the pipe. It must be noted that this formulation holds only for steady flow through pipes of unchanging diameter. It is obviously difficult to apply this formula quantitatively to flow through the vessels of the body since the flow may be pulsatile rather than steady, and since the most significant factor, the diameter of the tube, may vary from moment to moment as well as from point to point.

c used a consistent fall in flow until it ap- p oached values obtained with the rigid tube.

Effect of Cuff Pressure. As noted in section 2 above, an increase in cuff pressure acted to c mpress the collapsible tube under study a id thereby to reduce the delivery. For ex- a nple, a cuff pressure of 40 cm. water reduced t e flow from 25 ml. per second to 16 ml. per s cond (fig. 1). Likewise, raising the distal r sistance alone acted to reduce flow by virtue o the reduction in effective pressure head. H owever, a combination of these two flow r ducing effects sometimes produced apparent p radoxical results.

When the level of the outlet was raised while the cuff pressure was 40 cm., either there was no effect on flow, or sometimes the flow even increased significantly. Thus, raising the outlet 30 cm., and thereby reducing the effective pressure head from 130 to 100 cm. water caused an increase in flow from 16 to 18 ml. per second, an increase of 14 per cent. A further rise of 30 cm. in the height of the outlet had no effect on flow, even though the effective pressure head was now reduced to 70 cm. water.

These results appear paradoxical in that a greater flow through the system may be obtained for an effective pressure head of 70 cm. H_2O than is delivered for one of 130 cm. water. Similar effects were obtained at other cuff pressure levels (fig. 1).

The enhanced flow is apparently due to the distending effect of the outlet pressure on the collapsible rubber segment. This widening of the lumen of the tube accomplishes a reduction in resistance and energy loss. Despite the increased volume delivered, the velocity of the stream through the collapsible tube is reduced, and the tendency to flitter, which is velocity-dependent, is inhibited. This effect becomes apparent by noting that the flitter repetition rate, which was 26 per second when the outlet was 30 cm. below the collapsible tube, was reduced to 21 per second when the outlet was raised 20 cm.; it had fallen to 15 per second when the outlet was raised to the level of the tube, and with outlet at 30 cm. above the tube flitter ceased entirely. Similar effects noted at other cuff pressures are charted in figure 1. Even at very high cuff pressures (90, 100, 110 cm. water) the flow was relatively unchanged despite marked reductions in effective pressure heads. In these instances there was no apparent vibration of the tube. It would, therefore, appear that the reduction in effective pressure head was balanced almost exactly by the drop in resistance to flow due to the distention of the collapsible tube produced by the distal resistance. Generally, similar results were obtained in other experiments with the inlet pressure head set at 150, 100 and 50 cm. water.

It was sometimes possible to produce rather striking increases in delivery by raising the level of the outlet. One such set of data is given in table 1 in which the inlet pressure head was 100 cm. water. With the outlet set at the zero level, (i.e., at the level of the collapsible segment), the flow through the Penrose segment constricted with 90 cm. water cuff pressure was about 10 ml.; when the outlet level was raised 70 cm. water above the segment, the flow was increased to 17.5 ml. per second.

These data demonstrate that with certain relationships between driving pressure and degree of narrowing (cuff pressure), a rise in

TABLE 1.—*Effect of Outlet Height on Delivery Through A Collapsible Tube**

Outlet Height Above Collapsible Tube	Cuff Pressure				
	zero cm. H_2O	60 cm. H_2O	70 cm. H_2O	80 cm. H_2O	90 cm H_2O
cm.H_2O	*ml./sec.*	*ml./sec.*	*ml./sec.*	*ml./sec.*	*ml./sec.*
0	40	34	27	18	9.7
5	39	32	29	18	10.0
10	39	33	27	19	10.0
15	38	37	27	19	10.0
20	35	35	27	20	10.0
25	33	34	31	21	10.0
35	30	32	30	20	10.0
40	29	30	29	19	10.7
45	27	29	27	19	12.0
50	26	28	25	19	13.0
55	24	—	24	18	11.3
60	21	—	22	17	11.0
65	19	—	20	24	11.8
70	17	—	18	19	17.5
75	—	—	16	—	14.1

* Pressure head was kept constant at 100 cm. H_2O. Delivery is given in ml./sec.

outlet pressure can result in an enhanced flow. These effects are most probably due to the vessel distending effects of the distal resistance. Energy losses due to flow through a narrow tube as well as those due to the recurrent opening and closing of the vessel are thereby reduced or eliminated and present themselves as an increased delivery.

b. *Distal Resistance Due to an Orifice at the Outlet.* In these experiments a fixed orifice was used as the resistance to outflow from a collapsible tube. These orifices were smooth holes drilled into a plate of brass 25 mm. in thickness. The orifice was then fixed to the distal end of the elastic tube by means of a wide lumen brass pipe of 15 mm. diameter (fig. 2). The inlet pressure head utilized in these experiments was 125 cm. water.

When the cuff pressure was set at zero, the flow through the system was markedly affected by the outlet orifices. The flow through the system with outlet orifices of either 9.6 or 8.0 mm. diameter was 55.5 ml. per second. Outlet orifices of these sizes were so large that they imposed no significant resistance to outflow. For small outlet orifices, the flow was significantly reduced. Thus, an orifice of 6.4 mm. diameter permitted a flow of 53 ml. per second; an orifice of 4.8 mm. permitted 43.5 ml.; and an orifice of 32 mm. permitted 28 ml. to flow each second.

Application of cuff pressures less than 30 cm. water had no significant effect on flow with any of the orifices used. As the cuff pressure was raised higher than this level, flow fell off as expected (fig. 2). Thus, flow was progressively reduced as the cuff pressure was raised and the largest orifice (9.6 mm.) was used.

Delivery through the same system with an outlet orifice of 6.4 mm. diameter was unaffected by increases in cuff pressure until it was 45 cm. water. At this cuff pressure level, however, delivery was greater for the system with the smaller 6.4 mm. outlet orifice than for the 9.6 mm. orifice.

Similar effects were found with the smaller outlet orifices. This limited orifice was the apparent sole determining factor in volume delivered until the cuff pressure was raised to a critical level. At this level, however, the flow was greater for the smaller outlet orifices than for the larger outlet orifices.

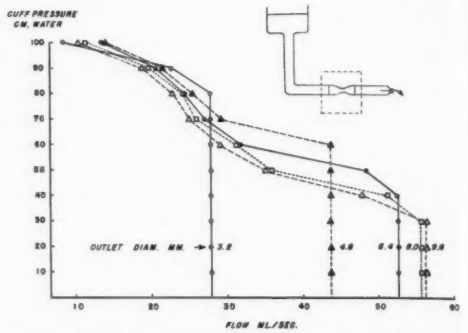


FIG. 2. The effect of various outlet orifices o delivery. Inset shows design of the experiment. Thi is similar to that given in fig. 1, except that th outflow resistance is provided by an orifice at th outlet, rather than by an overflow column.

The driving pressure was maintained at 125 cm. H_2O. The vertical axis gives the cuff pressure. The horizontal axis gives the delivery. The value given beside each of the lines denotes the diameter of the outlet orifice used in each case. The data show that for a given outlet orifice size, flow is unaffected by increasing cuff pressure until a critical value is reached. Above this value, for a given cuff pressure, flow falls off because of the greater resistance present in the collapsible Penrose tubing. It is to be noted that for certain cuff pressures, delivery through a narrow outlet orifice is greater than that obtained for a larger outlet orifice. For example, at a cuff pressure of 60 cm. water, delivery through an outlet orifice of 4.8 mm. diameter is 44 ml. per second, while that for an outlet orifice of 9.6 cm., flow is only 25 ml. per second. Discussed in the text.

This effect becomes clear when the data for each orifice was compared at specific cuff pressures. Thus, at a cuff pressure of 60 cm., flow was greatest (44 ml. per second) through the system with the outlet orifice of 4.8 mm., while it was only 28 ml. per second through the same system with the larger outlet orifice of 9.6 mm. By using the smaller outlet orifice, then, there was an increase in flow of over 50 per cent above that obtained by the use of the larger outlet orifice.

These data further clearly demonstrated that an outlet resistance, by acting as a distending force on a collapsible tube, could act "paradoxically" to increase flow.

It could be observed that when the enhanced flow occurred with the smaller outle

orifices, the flittering of the tube was suppressed. Distal resistances of the orifice type, like those due to the heightened column resistance also appear to operate by inducing a lack lateral pressure which distends the elastic segment and thereby inhibits flitter. The resistance to flow through this critical portion of the system is thus reduced, and the over-all resistance of the system is also lessened.

c. *Collapsible Tubes in Series.* Since situations may arise in which two successive segments of a vessel may be narrowed sufficiently so that both may be thrown into recurrent collapsibility (flitter), experiments were undertaken to test the effect of a distal or outlet resistance composed of a collapsible tube (fig. 3). In the description below, the first cuff and collapsible segment will be referred to as the *central* unit, and the second cuff and collapsible segment as the *distal* unit. The pressure head in this series of experiments was set at 136 cm. water.

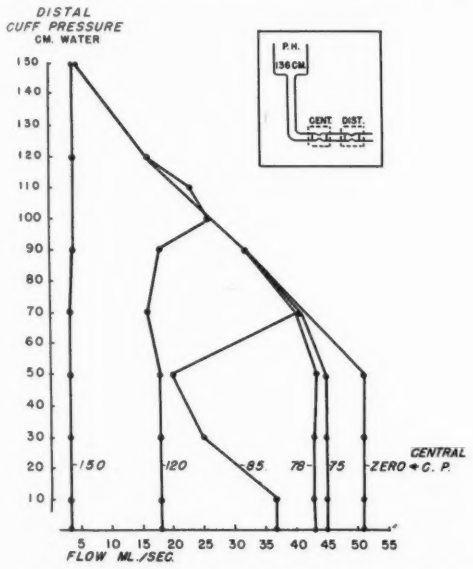


FIG. 3. The effect on delivery of two collapsible tubes in series. The design of the experiment is given in the inset. A driving pressure head of 136 cm. water was maintained throughout. Flow passing through the system was collected and measured. When the cuff pressure in both cuffs was zero (atmospheric), flow was 51 ml per second. The line at the extreme right shows the effect on an increase in only the distal cuff pressure. Values are given for data obtained with the central cuff pressure "C. P." set at various levels as noted. Data obtained at central cuff pressures of 75, 78, 85, 120 and 150 cm. H_2O are given for various levels of distal cuff pressure (vertical axis). Discussed in the text.

When the distal cuff was open to atmospheric pressure, increases in the central cuff pressure resulted, after reaching the critical value of 50 cm. water, in the occurrence of flitter in this segment, associated with a progressive reduction in delivery. These data are demonstrated in fig. 3 as values on the horizontal axis (distal cuff pressure equals zero). Under these conditions flow for a central cuff pressure of zero (line at extreme right of fig. 3) was 51 ml. per second. At a central cuff pressure of 75 cm. water, flow was 45 ml. per second; at a central cuff pressure of 85 cm., flow was 37 ml. per second, etc.

In the present study, the central cuff pressure was kept constant at a given value, and the distal cuff pressure was varied. The quantity of fluid delivered gave a measure of the energy losses due to the combined resistances of the two collapsible tubes.

When the central cuff pressure was set at values from zero to 75 cm. water, a rise in distal cuff pressure of 50 cm. water had no effect on flow. The effects of distal cuff pressures in the range 80 to 90 cm. water had special interest. Since the effects in these ranges were almost identical, they are given in fig. 3 as a single curve (labelled 85). As the distal resistance was raised from zero to 50 cm. H_2O, flow was markedly reduced by approximately half. A further increase in distal cuff pressure to 70 cm. water caused an increase in flow to values even greater than had been obtained when the distal cuff pressure was zero. Increases in distal cuff pressure above 70 cm. water caused a progressive reduction in flow.

A somewhat similar effect is illustrated for a central cuff pressure of 120 cm. water. An increase in distal cuff pressure had no effect on flow for the condition when the central cuff pressure was 150 cm. water.

Resonance effects in the flitter rates of the two collapsible segments appeared to be related to the anomalous flows obtained in the

80 to 90 cm. water distal cuff pressure levels. However, these were too complex to resolve with the stroboscope, and will probably require a more sensitive analytical procedure.

These data show, as with the other distal resistance arrangements discussed above, that under certain conditions an augmented flow may be obtained by increasing the resistance to outflow from a collapsed tube. This enhancement of flow is associated with effects on the rate of recurrent collapsibility and with a consequent reduction in the resistance to flow through the central collapsible segments.

Discussion

The body may be viewed as a collection of collapsible tubes which conduct fluid to various sites inside or outside the body. Among others, these include the blood vessels, the intestinal tract, the urogenital passages and the tracheobronchial airways. Elucidation of the special laws of flow through such collapsible tubes may have value in explaining some of the anomalous flow patterns and pressures in the various vessels of the body.[1, 2]

If the rules for flow through collapsible pipes can be considered to apply to flow through the collapsible tubes of the body, they may serve to uncover mechanisms of energy losses in the transport of fluid and in the production of sounds of various types. In previous studies we have suggested the possibility that occurrence of flitter in blood vessels and other tube systems of the body may be related to the general problems of murmur production.[1, 3, 4, 5]

The present results demonstrate that an increase in distal resistance beyond a collapsed or flittering tube can have very important effects on the ability of the pumping mechanism to push fluid through this vessel, as well as producing striking effects on the nature and frequency of the sounds which result. Thus, our data may be interpreted as suggesting that under certain conditions the addition of a second resistance may *reduce* the energy losses and thereby increase the apparent efficiency of a pumping organ, while incidentally inhibiting a murmur which may have been produced. The present data may thereby provide an insight into certain mechanisms associated with murmur production.[6]

The special mechanics of distal resistance may assist in explaining "crescendo-decrescendo" or "diamond shaped" murmurs of outflow stenosis[6] occurring during the rapid ejection phase. Thus, extrusion of blood through a stenotic aortic or pulmonic valve may produce flittering of the leaflets and result in a murmur. As the intraventricular pressure rises early in systole, flow is enhanced and the flitter repetition rate is increased. Toward the latter part of systole, the heightened arterial pressure may act as a distal resistance, reducing the flitter rate (decrescendo). Unpublished work on circulation models support these interpretations. It may also be suggested that the effect of outlet resistance may help explain findings in clinical situations with double stenosis or resistances.[7-10]

Respiratory intrathoracic pressure changes acting on the collapsible great veins also undoubtedly affect the ability of the venous blood to enter the chest and return to the heart, as indicated by the work of Holt,[2] Duomarco[11] and Brecher.[12]

The present studies demonstrate clearly that delivery through soft tubes differs significantly from flow patterns obtained with rigid tubes. Application of these mechanical principles to the collapsible tube systems of the body also may help to explain other special problems in the dynamics of flow.

Summary

The effect of an outlet resistance on flow through a collapsible tube was determined. When the collapsible tube is completely distended, it behaves similarly to a rigid tube, and an outlet resistance has the same effect as an equivalent reduction in driving pressure head.

However, when the collapsible tube is partially constricted, thereby reducing the flow and resulting in the production of the phenomenon of recurrent opening and closing (flitter) with fragmentation of the stream, murmur production and energy losses, an

or flow resistance may have no effect on flow, or may even enhance flow. This effect is apparently due to distention of the collapsed segment by the heightened lateral pressure; inhibition of the flitter phenomenon also contributes to the enhanced flow. It is suggested that these special dynamics may account for certain paradoxical findings in flow through partially stenosed vessels.

Summario in Interlingua

Esseva determinate le effecto exercite super le fluxo de liquidos via un collabibile tubo per un resistentia al bucca. Quando le collabibile tubo es completemente distendite, su reactiones es simile a illos de un tubo rigide, e un resistentia al bucca ha le mesme effecto como le equivalente reduction del propellente altitude manometric.

Del altere latere, si le collabibile tubo es partialmente constringite—de maniera que le fluxo es reducite e que consequentemente il occurre le phenomeno de recurrente aperturas e claudituras (palpitation) con fragmentation del fluxo, le production de murmure, e perditas de energia—alora un resistentia al bucca pote remaner sin effecto super le fluxo o pote mesmo accelerar lo. Iste effecto pare resultar del distention del collabite section de tubo per le augmentate pression lateral. Le inhibition del palpitation etiam contribue al acceleration del fluxo. Nos opina que iste observationes pote possibilemente servir a explicar certe constatationes paradoxe in le fluxo via vasos con stenosis partial.

Acknowledgment

I am indebted to Bert Swanson, D.D.S., and to Messrs. Ivan Manson and Matthew Thompson for valuable technical assistance.

REFERENCES

[1] Rodbard, S. and Saiki, H.: Flow through collapsible tubes. Am. Heart J., **46:** 715, 1953.

[2] Holt, J. P.: The collapse factor in the measurement of the venous pressure. Am. J. Physiol., **134:** 292, 1941.

[3] Rodbard, S.: Hydrodynamics illustrated in an artificial circulation model: varicosities, aneurysms, coarctation, sphygmomanometry, coronary flow. J. Appl. Physiol. **5:** 191, 1952.

[4] —: The significance of the intermediate korotkoff sounds. Circulation **8:** 600, 1953.

[5] —: Mechanism of the systolic murmur and the anacrotic incisura of aortic stenosis and coarctation. Am. J. Physiol. **171:** 761, 1952.

[6] —: Expanded time analysis of transients in heart sounds and murmurs. In preparation.

[7] Kirklin, J. W., Connolly, D. C., Ellis, F. H., Jr., Burchell, H. B., Edwards, J. E. and Wood, E. H.: Problems in the diagnosis and surgical treatment of pulmonic stenosis with intact ventricular septum. Circulation **8:** 849, 1953.

[8] Jacobson, G., Cosby, R. S., Griffith, G. C. and Mayer, B. W. Valvular stenosis as a cause of death in surgically treated coarctation of the aorta. Am. Heart J. **45:** 889, 1953.

[9] Humphreys, G. H., II, Powers, S., Fitzgerald, H. and Lanman, B. M.: Pulmonary valvulotomy. Surgery **35:** 9, 1954.

[10] Barach, A. L.: Physiologic Therapy in Respiratory Diseases. Philadelphia, J. B. Lippincott Co., 1948.

[11] Duomarco, J. L. and Rimini, R.: La presion intraabdominales en el hombre en condiciones normales y patologicas. Buenos Aires, El Ateneo, 1947.

[12] Brecher, G. A.: Mechanism of venous flow under different degrees of aspiration. Am. J. Physiol. **169:** 423, 1952.

CLINICAL PROGRESS

EDITOR: HERRMAN L. BLUMGART, M.D.

Associate Editor: A. STONE FREEDBERG, M.D.

Effect of Vitamin Deficiency on the Heart and Circulation

By MARION A. BLANKENHORN, M.D.

NOT much clinical progress can be reported in a field in which little is known, not much work going on and few patients are being observed. The situation has changed little from that described by this author in 1950: "That except for beriberi heart disease, which is known to be caused by diets deficient in thiamine, the matter to be discussed is in the realm of speculation or else in interesting animal experimentation."[1]

Beriberi was seldom described in American or in European literature. In Boston, New York, Philadelphia, Cincinnati and elsewhere, a few observers, having access to numerous patients, derelict because of chronic alcoholism, did describe a characteristic syndrome, which improved promptly after appropriate treatment. Before the pathogenesis of this syndrome could be discovered, it has practically disappeared, probably because of so-called diet reform and the better management of chronic alcoholism.

Where the disease was studied by elaborate physiological and biochemical methods, there was agreement about principal features in carefully selected patients.[2, 3, 4] These features were "high output failure" with accelerated peripheral circulation, elevated venous pressure, elevated right ventricular systolic and end diastolic pressure, lowered total pulmonary resistance and lowered total peripheral resistance with edema and no cyanosis. When patients with this disorder were observed during failure and immediately after the cessation of failure, no mechanism was discovered to explain either the cause of failure or the effect of therapy with thiamine, except that the patient usually completely recovered.

In fact, a contradiction of terms develops from this study. The heart is said to "fail" while it is doing more work and is circulating more blood when in failure than when out of failure. Although these tests before and after treatment have been done with due regard to the function of thiamine, which usually cures the disease, the riddle remains much as Wenckebach stated it in 1929 and in 1934, in much simpler clinical terms. For a lively discussion of this riddle the reader is referred to the work of Burwell and his co-workers.[2] Wenckebach and others proposed that vagus neuropathy was the mechanism, but no such lesion was found in man or experimental animals. Furthermore, such myocardial lesions as do occur in man are of a sort that could be a consequence of failure and are perhaps not the cause of failure. However, this writer, finding lesions in the upper segments of the cervical spinal cord in two typical patients,[5] has recently proposed that the mechanism is neurogenic, i.e. a disorder of vasomotion. This disorder of vasomotion is reflected in the circulation primarily and in the heart secondarily. When beriberi heart disease ends fatally, in the writer's experience, death is sudden and unexpected and no mechanism may be apparent at autopsy, especially, no great disruption of the heart muscle. No progress ha

From the Department of Internal Medicine, University of Cincinnati College of Medicine and Cincinnati General Hospital.

b en made beyond this speculation and the r ording of a few well studied examples of t e "riddle".

In the diagnosis of beriberi heart disease one s all item can be added to the stigmata of d ficiency disease which have been useful in it clinical recognition; nutritional type cir- r osis should be added to pellagra and periph- e al neuritis. The basis of this addition is a s tement from Dr. Bernard Black-Schaffer of t e Department of Pathology who restudied t e case material previously reported from the Cincinnati General Hospital as beriberi heart disease. Of ten records available for such review, five showed nutritional cirrhosis, two in the very early stages; three others showed nonspecific fibrosis of the liver and two showed neither fibrosis nor cirrhosis. He states: "There can be no doubt that the extremely high incidence of nutritional cirrhosis in this small group is of greatest significance." Because beriberi heart disease is the most clearly defined in the entire group of cardiocirculatory disorders, the diagnostic criteria, as published in 1946[5] and now generally accepted, are repeated below:

1. No other cause for heart disease found
2. Three or more months of thiamine-deficient diet
3. Signs of neuritis, pellagra or both
4. Enlarged heart with sinus rhythm
5. Dependent edema
6. Elevated venous pressure
7. Minor electrocardiographic changes
8. Recovery with decrease in heart size or autopsy consistent with beriberi heart disease, including nutritional type cirrhosis of the liver

If any new information about beriberi has come out of Korean prison camps, Brig. General Elbert DeCoursey of the Army Institute of Pathology has no knowledge of it. He reported, in a recent letter to me, that "the incidence of beriberi during World War II among American soldiers was negligible. There has been no revision of this statement".

In the difficult matter of deciding how much effect thiamine deficiency may have upon heart disease of any type, or perhaps all types, no clinical progress can be reported now. Biochemical testing of the patient to determine thiamine stores or thiamine needs is unsatisfactory. To prove the matter by giving thiamine or withholding it from the patient who has chronic failure is equally unsatisfactory in our experience. Recently, Wohl and his associates[6] have shown increased urinary output of thiamine, given as a test load to patients, who received a mercurial diuretic for treatment of chronic cardiac edema. In individual cases the matter is usually disposed of by giving thiamine in all prolonged and debilitating illnesses, especially where weight loss and diuresis could possibly cause a deficiency of any nutrient.

Vitamin E, in relation to myocardial disease, has recently received considerably more attention than has thiamine. In medical literature, the use of vitamin E (tocopherols) has reached the stage where large groups of patients are helped according to some observers, and equally large groups are found not helped by other observers.

The metabolism of tocopherols in relation to muscle development and muscle function has long been studied by Karl E. Mason and others. In primates, made deficient by diet manipulation, he found no disorder of the heart and circulation. In autopsy material from patients of various ages, dead of myocardial disease, he found no reduction of tocopherol content in various tissues, especially in the heart muscle tissue. In advance of publication,[7] he permits me to quote, from a personal communication: "These data in nowise suggest that tocopherols are useful in the management of acute myocardial failure." If the matter is to be settled by clinical trials already published, the most that can be said is "no progress." The interesting animal experiments, especially those dealing with the growth and development of skeletal muscle, do not throw light on the problems of heart disease in man.

Scurvy, although manifestly a disease involving capillaries in many sites with hemorrhage a conspicuous symptom, does not involve the heart and general circulation. In 1949 the author reported a ten year study of deficiency diseases in the Cincinnati General

Hospital[8] which included 33 cases of scurvy among adults. In this group there were six deaths. In none of the six did heart disease, that is so called "Scorbutic heart disease," cause or contribute to the death. Since that report, two other scorbutics were autopsied, as of June 1952, and in neither was there hemorrhage in the heart or pericardium. The incidence of degenerative heart disease among scorbutics is about the same as in the hospital population.

In the Cincinnati General Hospital we have seen several individuals in two attacks of severe and disabling scurvy but without any clear evidence of heart disease. Dependent edema is conspicuous; the nature of this edema in beriberi is not clear. Patients with scurvy die suddenly and unexpectedly in a manner suggesting vagal reflex and syncope. Such deaths are not associated with autopsy findings of heart disease. The vasomotor behavior of scorbutics is quite unlike that of beriberi patients except in this tendency to syncope. If any useful thing can be said now about the management of the heart and circulation in scurvy, it would be to guard against vagal stimulation.

In clinical and experimental study of such newer vitamins as folic acid, pyridoxine, vitamin B_{12} and even nicotinic acid, there is no hint that heart disease is caused, or preexisting heart disease aggravated, by them.

It should be pointed out here that pure forms of vitamin deficiency disease probably do not occur in nature and that more than one vitamin is usually concerned in any given patient. In nutritional failure, the effect on mineral metabolism is quite obscure. The patient's protein intake is often manifestly low and signs of hypoproteinemia are found. Tinsley Harrison has referred to this situation as "cardiac cachexia", a term that should call to mind the duty to study the patient's metabolic needs.

This report cannot consider low protein diets and heart disease, but it is inaccurate and misleading to write about the effects of vitamin deficiency on the heart and circulation when, in all probability, at least as far as can be proven, pure vitamin deficiency does not exist in nature and possibly not even under rigid experimental conditions. The writer is not aware of any clinical experiment that has attempted to apply such a grossly artificial approach to beriberi, scurvy, or any phase of heart disease as it occurs spontaneously.

There is, however, an increasing approach to the field of idiopathic heart diseases by searching for evidence of nutritional failure. In this class is endocardial sclerosis of infancy and "alcoholic heart disease" with mural thrombosis and postpartum myocardosis in young women.

The nutritional failure of the pregnant woman has been suspected as a cause of endocardial sclerosis of the infant as well as a cause of other forms of congenital heart disease. Postpartum myocardosis or myocarditis, as may be preferred, has been associated with multiple pregnancies and poor diets. This condition was described principally from the Charity Hospital in New Orleans, the Grady Hospital of Atlanta, the Cincinnati General Hospital and the Philadelphia General Hospital more than a decade ago. Now the several authors of such reports say, in personal communications, that the disease has become "very infrequent in recent years." This writer presumes that improved diets may be responsible for the disappearance of such idiopathic disease rather than that it has been renamed into some other entity.

Chronic alcoholism continues to be the main cause of nutritional failure in the United States. In a recent and personal communication, Dr. Hans Popper of the Hektoen Institute reports seeing idiopathic myocardial enlargement with mural thrombi in "repeated instances among chronic alcoholics." This disease, which is sometimes called alcoholic heart disease, is diagnosable but no specific therapy has been useful when the stage of endocardial sclerosis has developed. In this same class may be a disease described in South Africa and seen there in Bantus and other tribes, called cardiovascular collagenosis by Becker.[9] Becker found no cause for what he considered a specific disease entity. In a personal communica-

tion, January 1954, he gave reasons why he did not conclude that the cause was "primarily nutritional," but did consider that the nutritional aspects required further investigation. He had not seen it in Bantu children with kwashiorkor. Also in January 1954, a personal communication from Dr. V. N. Patwardhan, Director of the Nutrition Research Laboratories at Coonoor, S. India, reports that "endocardial fibroelastosis or sclerosis is a condition diagnosed very often at autopsy". It is known to occur in children between the ages of 3 days to 6 years and in three clinical patterns, the outstanding features of which are (1) sudden death in children within 24 to 48 hours after onset of respiratory distress; (2) prolonged progressive increase in dyspnea followed by cardiac failure and death; (3) repeated episodes of respiratory distress and cardiac failure sometimes lasting for months or years and showing cardiac hypertrophy.

By searching those spots in the world where nutritional deficiency diseases are common we may gain some hint as to the cause of our own idiopathic diseases of the heart.

REFERENCES

[1] Levy, R. L.: Disorders of the Heart and Circulation. New York, Thomas Nelson & Sons, 1951.

[2] Burwell, C. S. and Dexter, L.: Beriberi heart disease. Tr. A. Am. Physicians **60:** 59, 1947.

[3] Lahey, W. J.: Physiologic observations on a case of Beriberi heart disease. Am. J. Med., **14:** 248, 1953.

[4] Fowler, N.: Cardiac catheterization in the diagnosis of adult heart disease. Ann. Int. Med., **38:** 478, 1953.

[5] Blankenhorn, M. A.: Occidental beriberi heart disease. J.A.M.A., **131:** 717, 1946.

[6] Wohl, M. G., Shuman, C. R., Turner, R., and Fittipoldi, J. J.: Thiamine deficiency in organic heart disease. Circulation, **8:** 744, 1953.

[7] Mason, K. E.: The Vitamins. Vol. I, Harris, R. S. and Sebrell, W. H. In Press.

[8] Blankenhorn, M. A.: Deficiency diseases in the Cincinnati general hospital. J.A.M.A., **140:** 1315, August 1949.

[9] Becker, B. J. P., Chatgidakis, C. B., and van Liugen, B.: Cardiovascular collagenosis with parietal endocardial thrombosis. Circulation, **7:** 345, 1953.

ABSTRACTS

Editor: SAMUEL BELLET, M.D.

Abstracters

DAVID I. ABRAMSON, M.D., Chicago
ARTHUR BERNSTEIN, M.D., Newark
RUTH CORTELL, M.D., New York
A. D. DENNISON, M.D., Indianapolis
CHARLES D. ENSELBERG, M.D., New York
RAYMOND HARRIS, M.D., Albany
JOHN C. HARVEY, M.D., Baltimore
J. RODERICK KITCHELL, M.D., Philadelphia
ALDO A. LUISADA, M.D., Chicago
MORTON H. MAXWELL, M.D., Los Angeles
VICTOR A. MCKUSICK, M.D., Baltimore
MORTON J. OPPENHEIMER, M.D., Philadelphia
ALFRED PICK, M.D., Chicago
SEYMOUR H. RINZLER, M.D., New York
FRANCIS F. ROSENBAUM, M.D., Milwaukee
ELLIOT L. SAGALL, M.D., Boston
DAVID SCHERF, M.D., New York
JOHN B. SCHWEDEL, M.D., New York
CHARLES R. SHUMAN, M.D., Philadelphia
FRANKLIN SIMON, M.D., Newark
LOUIS A. SOLOFF, M.D., Philadelphia
RALPH M. TANDOWSKY, M.D., Hollywood
S. O. WAIFE, M.D., Philadelphia
MARTIN WENDKOS, M.D., Philadelphia
STANFORD WESSLER, M.D., Boston

BLOOD COAGULATION

Grossman, M. J.: The Quantitative Measurement of Heparin Induced Lipemia Clearing Activity of Plasma. J. Lab. & Clin. Med. **43:** 445 (Mar.), 1954.

A method for the quantitative measurement of fat clearing activity in plasma induced by heparin is presented. A synthetic fat emulsion, whose composition is given, substitutes for lipemic plasma. The method as studied employed normal rat plasma and plasma from heparin-injected rats. The measurement of clearing activity is based upon reduction of turbidity of this mixture measured in the spectrophotometer. Clearing activity is expressed as the reciprocal of the time in seconds $\times 10^3$ of a 0.15 fall in optical density for a standard volume of the mixture of synthetic fat emulsion-plasma. It was shown that the clearing activity of rat plasma is thermolabile, that it is maximal at 20 to 25 C., that it increases logarithmically with the dose of heparin administered until it reaches maximum activity at any dosage above 1.0 mg. heparin per kilogram of body weight, and that it is unrelated to concentrations of fat in the synthetic emulsion up to 4 per cent.

HARVEY

Howell, D. and Kyser, F. A.: The Effects of Anticoagulant Therapy Upon the Development of Mural Thrombosis Following Myocardial Infarction. Ann. Int. Med. **40:** 698 (Apr.), 1954.

At the Evanston Hospital, between 1948 and 1952, autopsy examination was made of 158 patients with recent myocardial infarction. Those who had survived less than 72 hours were excluded from this study because the cases were analyzed with regard to the possible benefits from anticoagulant therapy. This report is therefore based upon the findings in 132 patients, 98 of whom did not receive anticoagulants. Of these 98 patients, 53 had mural thrombi, with four of the mural thrombi being in the auricle and the remainder in the ventricle. Of the 34 patients who did receive anticoagulants, 10 had mural thrombi, two of these being intra-auricular and eight being intraventricular. The degree of the prothrombin control did not appear to influence this development of mural thrombosis in patients treated with anticoagulants. Embolic accidents (cerebral and pulmonary) occurred more than twice as often in individuals with mural thrombosis as in those without.

WENDKOS

Chalmers, T. C., Bigelow, F. S., and Disforges, J. F.: The Effects of Massive Gastrointestinal Hemorrhage on Hemostasis. II. Coagulation Factors. J. Lab. & Clin. Med. **43:** 511 (Apr.), 1954.

In 27 patients with cirrhosis and 45 patients with normal liver function, all of whom had massive gastrointestinal hemorrhage, studies were made to determine the coagulation factors. These were only slight abnormalities in the coagulation factors. There was a lowered prothrombin time but normal prothrombin consumption. Fibrin formation was abnormal in the cirrhotics. None of these changes, however, could be correlated with amount or duration of hemorrhage, presence or absence of shock. It is felt that hemostasis is maintained adequately during gastrointestinal hemorrhage even when severe liver disease is present.

HARVEY

CONGENITAL ANOMALIES

Donald, D. E., and Kirklin, J. W.: Experimental Production of Progressive Pulmonic Stenosis. Thoracic Surg. **27:** 149 (Feb.), 1954.

Bands of cellophane were wrapped around the main pulmonary artery in dogs in order to produce progressive pulmonic stenosis. It was noted that the major factor in eventual production of right ventricular hypertension resided in the degree of initial constriction produced at operation. If this was insufficient, the latter stricture did not offer enough resistance to outflow from the right ventricle to promote hypertension, while if it was too severe, the ventricle was unable to maintain circulation against the excessive load.

ABRAMSON

Sloan, R. D., Hanlon, C. R., and Scott, H. W., Jr.: Tuberculosis and Congenital Cyanotic Heart Disease. Am. J. Med. **16:** 528 (Apr.), 1954.

The authors reviewed the chest roentgenograms of 800 patients who were operated upon for pulmonary stenosis in an attempt to ascertain the incidence of pulmonary tuberculosis among patients with congenital cyanotic heart disease. Although 39 patients presented radiologic findings consistent with pulmonary tuberculosis, further study excluded tuberculosis in 24 instances. In the 800 patients the maximal possible incidence of tuberculosis by these criteria is less than 2 per cent. The data indicate that the incidence of pulmonary tuberculosis in patients with congenital cyanotic heart disease is not strikingly high. Likewise, available data do not suggest that surgical therapy increases the risk of concomitant tuberculosis in these patients. Experimental work in monkeys infected with tuberculosis has demonstrated a distinctly unfavorable result which occurs when a tuberculous lung is perfused with systemic arterial blood. Presumably it is the "arterialization" of the infected pulmonary tissue which results in aggravation of the infection, since the growth of the tubercle bacillus may be promoted by the high oxygen concentration. In patients with pulmonary tuberculosis and inadequate pulmonary blood flow due to pulmonary stenosis of the type accompanying the tetralogy of Fallot, the authors recommend an end-to-end or end-to-side anastomosis on the side opposite the major tuberculous involvement. Alternatively, the direct (Brock) attack on the point of intracardiac obstruction might be performed to increase the blood flow to both lungs without raising the oxygen saturation of the perfusing blood. Finally, an end-to-end (or end-to-side) anastomosis on the side of the major tuberculous involvement might be performed and followed by a resection of the appropriate amount of involved pulmonary tissue.

HARRIS

Goldberg, H., Bakst, A. A., and Bailey, C. P.: The Dynamics of Aortic Valvular Disease. Am. Heart J. **47:** 527 (Apr.), 1954.

The circulatory dynamics in 40 patients with aortic valvular disease was studied by catheterization of the right side of the heart and peripheral arterial pressure curves. Twenty-six patients had predominant aortic stenosis; 14 had predominant aortic regurgitation. Measurements were made at rest and during exercise. The response to the Valsalva maneuver was determined. Although obstruction and regurgitation at the aortic orifice differ basically, the circulatory patterns were in many respects similar. The resting cardiac output is generally within normal limits. Although a rise in the cardiac output is the rule during exercise, it is frequently less than would be expected. The limited cardiac output either at rest or during activity may be due to: (a) the presence of coexisting mitral disease; (b) left ventricular failure; and (c) the lesion (stenosis or regurgitation), per se. The pulmonary circulation is usually normal. Pulmonary hypertension, when present, may be due to several factors: (a) left ventricular failure; (b) coexisting mitral stenosis; or (c) pulmonary vascular changes. Pulmonary vascular changes may be important contributing factors in the production of right ventricular failure in some cases. The peripheral arterial pressure curves are characteristic in aortic stenosis and aortic regurgitation. Marked changes are noted in the brachial arterial pressure tracings during and immediately following the Valsalva maneuver. It is suggested that this maneuver may be helpful in bringing out the anacrotic phenomenon and elucidating certain findings in the resting peripheral pressure curve.

RINZLER

Bahn, R. C., Sanes, S., Juvelier, B. W., and Urban, S. T.: Presubclavian Coarctation of the Aorta. Report of a Case with Aneurysm of the Descending Thoracic Aorta and Bicuspid Pulmonary Valve Complicated by Pregnancy. Am. Heart J. **47:** 444 (Mar.), 1954.

A case of aortic narrowing proximal to the left subclavian artery, with a large saccular aneurysm involving the descending thoracic aorta and a bicuspid pulmonary valve, is presented in a patient whose cardiovascular lesion was complicated by pregnancy. The patient entered the hospital in mental confusion and died six weeks later.

RINZLER

Clagett, O. T., Kirklin, J. W., and Edwards, J. E.: Anatomic Variations and Pathologic Changes in Coarctation of the Aorta. A Study of 124 Cases. Surg., Gyn. & Obst. **98:** 103 (Jan.), 1954.

A study of the anatomic and pathologic changes in coarctation of the aorta was made on a series of

124 cases. Of this number, 42 were females and 82 were males; no explanation was available for the sex difference. Histologic examination of the involved segment of aorta did not support the view that the coarctation is related to overgrowth of tissue of the ductus arteriosus into the aortic wall. The obstruction was usually found just distal to the origin of the left subclavian artery and, on occasion, proximal to this vessel. Associated anomalies, such as a patent ductus arteriosus, were frequently noted.

In 11 instances (8.8 per cent) the lesion was believed to be inoperable. However, the authors, in retrospect, felt that in some of these, aortic grafts could have been used. Unfortunately, they were not available at the time of the study.

ABRAMSON

Moffitt, G. R., Jr., Zinsser, H. F., Jr., Kuo, P. T., Johnson, J., and Schnabel, T. G.: Pulmonary Stenosis with Left to Right Intracardiac Shunts. Am. J. Med. **16:** 521 (Apr.), 1954.

The authors present clinical and catheterization data obtained in six patients with pulmonary stenosis and left-to-right intracardiac shunts of blood. In four patients there were coexisting ventricular septal defects; in two patients atrial septal defects were demonstrated. The factors governing the direction of intracardiac shunts in such patients include the degree of pulmonary stenosis, the degree of compensation of the right ventricle, and, in those with associated ventricular septal defects, the degree of dextroposition of the aorta. A predominant left-to-right intracardiac shunt in the presence of pulmonary stenosis should be evaluated as a possible contraindication to valvulotomy. It might be wiser to defer operation in such patients until improved technics with direct visualization permit better reconstruction of the outflow tract and simultaneous closure of the septal defect. For the present, valvulotomy might be restricted to those patients with pulmonary stenosis, with marked elevation of the right ventricular pressure and without evidence of a predominant left-to-right intracardiac shunt.

HARRIS

Dixon, A. St. J.: Juxtaposition of the Atrial Appendages: Two Cases of an Unusual Congenital Cardiac Deformity. Brit. Heart J. **16:** 153 (Apr.), 1954.

Two hearts with the atrial appendages lying side by side are described. In one, they were to the right of both great vessels; in the other, to the left. Ten other instances are summarized of juxtaposition of the atrial appendages lying to the left of the great vessels. The following defects are constant for this group: atrial septal defect or defects, ventricular septal defect, stenosis of the pulmonary trunk and partial transposition of great vessels. An accessory septum in the right ventricle and tricuspid thickening or atresia may be seen in some.

SOLOFF

Dexter, L.: Cardiac Catheterization in Diagnosis of Congenital Heart Disease. Minnesota Med. **37:** 116 (Feb.), 1954.

Notable improvement in the diagnosis of congenital heart disease has been achieved as a result of the introduction of cardiac catheterization. The purpose of this communication is to point out information that can be obtained by this procedure as well as to indicate its shortcomings. Catheterization may provide useful data by the following means: (1) the demonstration fluoroscopically of the introduction of the catheter into an abnormal pathway; (2) the demonstration of an abnormal pressure gradient across the pulmonic or tricuspid valve, indicative of stenosis of the valve; (3) the demonstration of the identity of the systolic pressures in the right ventricle and brachial artery, indicative of an overriding aorta or a functionally similar condition; (4) the demonstration of the presence of arterialized blood in one of the chambers of the right side of the heart or in the pulmonary artery, indicative of a left-to-right shunt; and (5) the demonstration of arterial oxygen unsaturation not corrected by the administration of 100 per cent oxygen of a right-to-left shunt. The latter procedure does not involve catheterization, but is often carried out in conjunction with it.

In addition, the determination of flows, pressures, and resistances at rest and during various physiologic stresses, permits a better appreciation of the abnormal physiologic processes and a deeper insight into the clinical course and natural history of the disease.

BERNSTEIN

Van Buchem, F. S. P., Nieveen, J., and Marring, W.: Cor Triloculare Biatriatum. Cardiologia **24:** 134 (Fasc. 3), 1954.

A case is described of a 31 year old woman with late cyanosis, a loud systolic murmur left of the sternum, incomplete right bundle-branch block indicated in the electrocardiogram, a normal heart silhouette and marked pulmonary vascular markings shown by x-ray film. The diagnosis of a cor triloculare biatriatum could be established during life with the help of cardiac catheterization and angiocardiography. The oxygen saturation and systolic pressure were equal in the (common) ventricle, the aorta, and the pulmonary artery. Prominent filling of the pulmonary arteries and simultaneous faint visualization of the aorta in angiocardiograms suggested that the big vessels were transposed and that the aorta arose from a rudimentary right ventricle. The literature on this condition is sum

marized and the clinical picture, prognosis and operability are discussed.

PICK

Berkowitz D., and Likoff, W.: Mitral Stenosis Complicating Situs Inversus: A Case Successfully Treated by Commissurotomy. Ann. Int. Med. **40:** 784 (Apr.), 1954.

A 32 year old housewife was admitted to the Thoracic Surgical Department of Hahnemann Hospital on Nov. 17, 1952. There was no history of rheumatic fever during childhood or thereafter. At the age of 26, during the third trimester of her first pregnancy, the patient developed nocturnal dyspnea with hemoptysis, but nevertheless went on to a normal delivery with no postpartum complications. Thereafter she remained in good health until 18 months before admission, when she developed progressive exertional dyspnea and marked fatigue. There was no history of peripheral edema or embolic episodes. Physical examination revealed a well-developed and well-nourished woman who appeared in good health. The blood pressure was 110/80 mm. Hg. The rhythm was regular. The point of maximal impulses was localized at the right fifth intercostal space beyond the midclavicular line. At this area the first sound was sharp and a presystolic accentuation of a midlate diastolic murmur was heard. It was also of interest to note that this same murmur could be heard with no difficulty over the precordium at the usual mitral area. The second pulmonic sound was accentuated 2 plus and was heard at the second right intercostal space. The remainder of the examination was normal. X-rays of the heart showed dextrocardia with cardiac enlargement and a typical mitral contour. The left auricle and right ventricle were enlarged 1 to 2 plus. An electrocardiogram taken with the precordial leads over the right side revealed dextrocardia with evidence of right ventricular hypertrophy and strain. Cardiac catheterization demonstrated the presence of pulmonary hypertension. Because of the severe degree of pulmonary hypertension demonstrated by catheterization and the progressive nature of the symptoms a mitral commissurotomy was performed. Following commissurotomy, the valve admitted two fingers with ease. The postoperative course was uneventful.

WENDKOS

Haronofsky, I. D., and Adams, P., Jr.: Resection of an Aortic Coarctation in a Two Week Old Infant. Ann. Surg. **139:** 494 (Apr.), 1954.

The authors performed a resection of an aortic coarctation in a two-week old infant who was in uncontrollable heart failure. A successful end-to-end anastomosis was accomplished. A follow-up study two years later revealed the child to be in excellent condition.

It is suggested that in the small group of babies under 1 year of age who have an aortic block and cardiac embarrassment which does not respond to medical therapy, surgical intervention is indicated.

ABRAMSON

Goldring, D., Rogers, H. M., Jr., Ter-Pogossian, M., Seaman, W. and Behrer, M. R.: Radiocardiography in Congenital Heart Disease. J. Pediat. **44:** 392 (Apr.), 1954.

Preliminary observations were presented on 22 normal children and 100 children with congenital heart disease studied by means of radiocardiography. The radiocardiograms obtained from most children with congenital heart disease were different from those obtained from the normal control group. The method may be useful in differentiating patients with Eisenmenger complex from those with tetralogy of Fallot. Although the exact physiologic phenomena responsible for the types of curves obtained are not known, preliminary evidence suggests that the radiocardiogram is predominantly a reflection of blood flow in the right heart.

MAXWELL

Swan, H. J. C.: Diagnostic Applications of Indicator Dilution Curves in Heart Disease. Minnesota Med. **37:** 123 (Feb.), 1954.

Analysis of indicator-dilution curves based on differences in contour and time relationships offers a new tool in the study of heart disease. In particular, the method permits a more detailed study of the dynamics in congenital heart disease and, therefore, better appraisal of the anatomic defect present. In this presentation certain of the concepts basic to the technic have been outlined. In the individual case, the physician at catheterization makes use of the methods as he proceeds with the study, since careful selection of sites of injection on the basis of data being obtained during the procedure will allow a more precise diagnosis to be made. In the cardiac catheterization laboratory of the Mayo Clinic, this technic is an established, integral part of the routine investigation of the majority of cardiac patients studied. In these days of the increasing possibility of successful surgical therapy for congenital heart disease, the added accuracy of diagnosis provided by the technic has proved to be of practical value.

BERNSTEIN

CONGESTIVE HEART FAILURE

Schwartz, W. B., and Relman, A. S.: Electrolyte Disturbances in Congestive Heart Failure. J. A. M. A. **154:** 1237 (Apr. 10), 1954.

Disturbances in electrolyte and water metabolism may often be of critical importance in determining the prognosis and continued response to therapy in congestive heart failure. This article briefly outlines the various iatrogenic and spontaneous disorders of electrolyte metabolism that have been observed in cardiac patients. Hypochloremic al-

kalosis due to excessive loss of chlorides from mercurial diuresis is important because it may result in nonresponsiveness to further mercurial diuresis. It may be repaired by the use of ammonium chloride; the use of dilute hydrochloric acid by mouth, or 1 per cent solution of ammonium chloride in 5 per cent glucose solution has been found to be safe and effective. Hyponatremia (the low-salt syndrome) is usually attributed to salt depletion resulting from excessive use of a low-salt diet and mercurial diuretics, but it often occurs in patients who have received little or no treatment and have no obvious cause for sodium deficiency. In these cases it is a bad prognostic sign, since many of these patients succumb regardless of the treatment used. Hyponatremia, associated with external losses of sodium, caused by vomiting, sweating, diarrhea, thoracentesis or paracentesis, usually responds well to infusion of hypotonic sodium chloride solution. Elevation of the plasma bicarbonate concentration with reciprocal reduction in chloride concentration may occur in cardiac patients from two different mechanisms. Often a metabolic alkalosis is due to mercurial diuresis, or the bicarbonate concentration of the blood may become elevated as the result of primary lung disease and reduced pulmonary ventilation. Here the blood becomes more acid. In the latter type the use of Diamox, a new carbonic anhydrase inhibitor, is useful. On occasion the use of ammonium chloride may result in azotemia, severe hypochloremic acidosis, and coma. This usually occurs in patients with renal disease or in patients treated continuously for weeks at a time. The hazards of ammonium chloride intoxication emphasize the fact that this drug cannot be used indiscriminately in congestive heart failure. The use of mercurial diuretics or ammonium chloride may occasionally produce the clinical syndrome of potassium depletion, especially if the food intake is poor. The chief importance of potassium deficiency is its occasional association with digitalis intoxication. One of the commonest reactions to cation exchange resins is hyperchloremic acidosis. In patients with good renal function acidosis is rarely severe enough to be a problem, but severe acidosis may develop in patients with renal disease who cannot rapidly remove the acid released by the resins. Symptoms and signs are similar to those of ammonium chloride poisoning. Although experience with Diamox is as yet too brief to permit broad generalization, it appears unlikely that acidosis from this drug will often be a serious problem. The effect of Diamox on serum bicarbonate concentration appears to limit its further activity so that the diuretic and acidifying actions of the drug diminish as the serum bicarbonate is lowered. Total diuresis produced by Diamox in severe congestive failure without cor pulmonale usually has not been significant.

KITCHELL

Bernstein, L. H. T., and Evans, J. M.: Treatment of Edema with Cation Exchange Resins, Including Certain Hormonal Observations. Ann. Int. Med. **40:** 698 (Apr.), 1954.

Of 11 ambulatory patients with the edema of chronic cardiac decompensation treated with cation exchange resin, good diuresis occurred in eight and maintenance in better cardiac compensation with fewer mercurial injections was obtained. The three agents used contained 1 to 2 mEq. of potassium per gram of resin. The concentration of serum sodium and potassium did not vary substantially from control or normal values during administration. The hydrogen-potassium carboxy resin and the ammonium potassium carboxy resin produced compensated acidosis in the majority of instances. The side reactions during resin therapy included acidosis, weakness, anorexia, nausea, vomiting, diarrhea, or constipation, and digitalis intoxication. The incidence of complications varied with the form of resin employed. Careful observation of patients receiving these agents is essential. Seven of 25 resin trial periods were unsuccessful in this study. The causes of failure were not established but may include lack of cooperation by the patient excessive sodium intake, persistent nausea and vomiting, inadequate resin dosage and probable undetermined intrinsic factors. The quantitative relationships of weight changes and urinary excretion of sodium and potassium before, during and after resin therapy were evaluated. During resin therapy there is rapid weight loss with diuresis of sodium and potassium. It is postulated that cation exchange resins induce diuresis by preventing absorption of a relatively small fraction of sodium in the gastrointestinal tract, thus favorably influencing an individually determined critical level of sodium excretion by the kidney. Hormonal factors are also operative, inasmuch as excretion of 17-ketosteroids increased in association with the diuresis of resin therapy. Cation exchange resins are valuable agents for the treatment of the edema of chronic cardiac decompensation and hepatic cirrhosis, particularly in nonhospitalized patients. It appears that this form of treatment is supplementary to the traditional methods of edema control.

WENDKOS

Schreiber, S. S., Bauman, A., Yallow, R. S., and Berson, S. A.: Blood Volume Alterations in Congestive Heart Failure. J. Clin. Invest. **33:** 578 (Apr), 1954.

The authors reinvestigated the status of the blood volume in heart failure by performing simultaneous red cell and plasma volume determinations before and after compensation in a group of patients with decompensated heart disease. Erythrocyte volumes were measured by P^{32}-tagged red cells and plasma volumes by the use of solutions of I^{131} labeled human serum albumin.

In 22 of the 26 patients studied, compensation was accompanied by a decrease in total blood volume ranging from 3.5 to 23 per cent. In four subjects, however, there was an increase in total blood volume. The decrease in the blood volume in the majority was chiefly attributable to a loss of plasma volume, but, in most of these, a fall in red cell volume was also noted. The ratio of the total body relative cell volume (which is the red cell volume divided by the red cell volume plus plasma volume) to the venous hematocrit value was observed to be decreased in cardiac failure and to rise with compensation in most cases.

The authors conclude that the calculation of plasma volumes from measured red cell volumes and hematocrit readings alone may not detect significant changes.

WAIFE

CORONARY ARTERY DISEASE

Wégria, R., Frank, C. W., Misrahy, G. A., Wang, H., Miller, R. and Case, R. B.: Immediate Hemodynamic Effects of Acute Coronary Artery Occlusion. Am. J. Physiol. **177:** 123 (Apr.), 1954.

Myocardial infarction was produced by ligation of the left anterior descending coronary artery. In most cases there was an early decrease in heart output and arterial blood pressure. In the majority of experiments these two parameters gradually returned to or toward control values. Total peripheral resistance was either unchanged or increased. Fall in pressure was always due to decreased output. In many cases the decreased output was of sufficient magnitude to permit a fall in blood pressure even though peripheral resistance increased.

OPPENHEIMER

Coe, W. S.: Cardiac Work and the Chair Treatment of Acute Coronary Thrombosis. Ann. Int. Med. **40:** 42 (Jan.), 1954.

Six patients from the medical wards of the Louisville General Hospital were studied. The first two patients were convalescing from acute infections. The third was a controlled epileptic. These first three had normal cardiovascular systems. The last three were diagnosed as cases of arteriosclerotic heart disease.

The last three had enlarged hearts, determined by teleradiography, and all had abnormal electrocardiograms compatible with a diagnosis of coronary artery disease. One patient was mildly decompensated at the time of study. The other two were in moderate failure at the time of study. Each patient was studied while in the basal state.

The patients were allowed to rest for 45 minutes in the recumbent position on a heavily padded fluoroscopy table. A cardiac catheter was then placed in the pulmonary artery by the usual technic. As soon as the patient was in a "steady state" a cardiac output determination was made by the dye-injection method. The dye (T 1824) was injected into the pulmonary artery and serial arterial samples were obtained from an indwelling radial artery cannula.

The patient was then helped into a padded armchair where he remained for 30 minutes and the cardiac output and pressure measurements were repeated. None of the six patients demonstrated any evidence of anxiety during the studies conducted.

In each patient the calculated cardiac work was less in the armchair posture. The mean reduction in the work of the heart amounted to 23 per cent. This gives support to the clinical observations of Levine that patients with acute coronary thrombosis are often benefited by the "chair treatment."

DENNISON

Burchell, H. B., Klakeg, C. H., Pruitt, R. D., and Berkson, J.: Prognosis in Coronary Heart Disease in Relation to the Hypoxia Test. Cardiologia **24:** 129 (Fasc. 3), 1954.

A statistical analysis is presented of survival rates of 158 patients with clinically diagnosed coronary disease, 138 of whom were followed for five or more years after the performance of a hypoxia test. In 100 of these patients the test was positive and in 58 it was negative. The average age in both groups was the same (49.1 years). One hundred forty-seven of the patients were males and 11 were females.

The evaluation of the data led to the conclusion that, in spite of a higher mortality rate in the group of patients with positive hypoxia tests, this procedure could not significantly differentiate patients with coronary disease with respect to longevity and prognosis.

PICK

ELECTROCARDIOGRAPHY, VECTORCARDIOGRAPHY AND BALLISTOCARDIOGRAPHY

Roesler, H., and Dressler, W.: Transient Electrocardiographic Changes Identical with Those of Acute Myocardial Infarction Accompanying Attacks of Angina Pectoris. Am. Heart J. **47:** 520 (Apr.), 1954.

The authors report instances in two patients (ages 55 years and 68 years, respectively) who, during spontaneous attacks of angina pectoris, showed transient changes in the electrocardiogram usually associated with myocardial infarction. The changes disappeared rapidly. These changes included significant Q deflections associated with elevation of the S-T segment or inversion of T_1. The authors conclude that transient coronary insufficiency, if of great magnitude, may in rare instances cause similar temporary changes usually associated with myocardial infarction.

RINZLER

Carlsten, A., and Rudhe, V.: An Electrokymographic Study of Auricular Arrhythmia in Total Heart Block. Acta radiol. **41:** 316 (Apr.), 1954.

Two cases with total heart block and a varying auricular rate, were studied by means of simultaneous registration of the electrocardiogram, the phonocardiogram and the right auricular electrokymogram. In both cases there was a tendency for longer auricular intervals following deep deflections in the electrokymogram and deeper deflections in the electrokymogram following longer auricular intervals. This suggests that the auricular arrhythmia in total heart block is influenced by the filling and emptying of the auricles.

SCHWEDEL

Prinzmetal, M., Shaw, C. McK., Jr., Maxwell, M. H., Flamm, E. J., Goldman, A., Kimura, N., Rakita, L., Borduas, J., Rothman, S., and Kennamer, R.: Studies on the Mechanism of Ventricular Activity. VI. The Depolarization Complex in Pure Subendocardial Infarction; Role of the Subendocardial Region in the Normal Electrocardiogram. Am. J. Med. **16:** 469 (Apr.), 1954.

The production of pure chronic and acute subendocardial infarction in dogs by coronary artery ligation and burns, respectively, did not significantly alter the depolarization complex. Contrary to classic electrocardiographic theory, the R wave recorded over normal hearts was found to result from activation of the outer ventricular layers and was not significantly affected by subendocardial depolarization. Bipolar tracings indicated that depolarization of the outermost few millimeters of the ventricle is primarily responsible for the normal surface R wave. Approximate rates of intramural depolarization were measured by means of cathode-ray oscillograms. Depolarization of the inner ventricular layers was found to occur at rates approximating several thousand millimeters per second. The outer ventricular layers depolarized at rates of about 300 to 500 mm. per second. Subendocardial depolarization may fail to affect the electrocardiogram, because it occurs too rapidly to be recorded. The absence of abnormal Q waves over subendocardial infarcts in the present series is attributed to the fact that the outer ventricular layers remained entirely intact and normal R waves, resulting from depolarization of these layers, are recorded. Since the inner ventricular myocardium appears to have little or no effect on the electrocardiogram, clinical electrocardiography is of limited value in the diagnosis of myocardial disease which does not involve the superficial layers of the heart.

HARRIS

Mattoli, G., and Angelini, F.: The Study of the Electrical Systole (Q-T) in Diphtheria. Cuore e circolaz. **37:** 321 (Dec.), 1953.

The electrical systole was studied in 132 cases of diphtheria. The results obtained by using the formula of Bazett were compared with those obtained by the formula of Ashman, and it was concluded that the latter are more accurate.

The Q-T interval was found to be prolonged in diphtheria. The variations of its duration, in addition to their diagnostic value, also assume a prognostic significance in a large number of cases.

AUTHORS

Gross, D.: Quantitative Correlation between the Length of the T-P Interval and the Cardiac Cycle. Am. J. Physiol. **177:** 121 (Apr.), 1954.

In resting subjects the T-P interval is 0.50 second less than the corresponding cardiac cycle. When this interval is expressed as a percentage, it shows a marked change with variation in heart rate.

OPPENHEIMER

Van Lingen, B., Gear, J. H., Whidborne, J., and Lister, M.: The Ballistocardiogram in Aortic Stenosis. Am. Heart J. **47:** 560 (Apr.), 1954.

Low-frequency critically damped and high-frequency ballistocardiograms were analyzed in three cases of aortic stenosis and in 14 cases of combined aortic stenosis and incompetence. These findings were compared with the ballistocardiograms of normal subjects and of patients with other types of heart disease including syphilitic aortic incompetence. Angulation or bowing of the J-K segment of the low-frequency ballistocardiogram was greater than that observed in the control group in 11 of the 17 cases of aortic stenosis and combined aortic stenosis and incompetence. This finding was attributed to the aortic stenosis in view of its absence in cases of pure aortic incompetence due to syphilis and other types of heart disease. The degree of angulation of the J-K segment of the low-frequency ballistocardiogram correlated roughly with the extent of aortic valvular stenosis. A small K wave and a deep M wave in the high-frequency ballistocardiogram were found in 10 of the 17 cases of aortic stenosis or combined aortic stenosis and incompetence. This pattern did not appear to be as specific for aortic stenosis as that observed in the low-frequency ballistocardiogram since it was also seen in some normal subjects and in patients with coarctation of the aorta and other types of heart disease.

RINZLER

Elek, S. R., Allenstein, B. J., Kornbluth, A. W., Griffith, G. C., and Levinson, D. C.: The Spatial Vectorcardiogram in Myocardial Infarction Typified by Prominent R Waves in Leads aV_R and V_1. Am. Heart J. **47:** 477 (Apr.), 1954.

This report emphasizes the vectorcardiographic features and significance of myocardial infarction distinguished by the presence of prominent R waves in leads aV_R and V_1. This usually occurs in antero-

lateral or posterolateral myocardial infarction. Five male patients, ranging in age from 39 to 59 years were chosen. Each had had clinical evidence of myocardial infarction and confirmatory electrocardiograms and laboratory data.

Vectorcardiographic studies revealed that the spatial vector loop was in the right superior anterior octant in three patients, the right superior posterior octant in the fourth patient, and the left superior posterior octant in the fifth patient. The horizontal plane vector loop was strikingly displaced to the right in four of the five patients. The development of tall R waves in Leads aV_R and V_1 is shown in two patients. Evidence is presented that these prominent R waves occur in either antero- or posterolateral wall myocardial infarction and that the infarct must be large in ratio to the remaining myocardium.

RINZLER

Gross, D.: The Duration of the T Wave and Its Relation to the Cardiac Rate in Healthy Adults. Am. Heart J. **47:** 514 (Apr.), 1954.

Lead II of the electrocardiographic records of clinically normal subjects was used to measure the length of cardiac cycle, the Q-T interval and the height and duration of the T wave. Records were divided into groups of 30 on the basis of cardiac rates of 51 to 120. The results were based on measurable records.

The duration of the T wave is determined mainly by the length of the cardiac cycle; this correlation is a quantitative one. The height of the T wave influences its duration in a definite sense but not in a predictable form. The duration of the T wave can only be evaluated in relation to the cardiac cycle, in a manner similar to that of the Q-T interval. The duration of the T wave presents the following two quantitative correlations: (a) on an average, it is one-hundredth of a second less than the one-half duration of the corresponding Q-T interval; $T\ dur. = Q\text{-}T/2 - 0.01$; (b) on the other hand, its relation to the cardiac cycle is expressed by the equation. $T\ dur. = 0.08 + RR/10$.

RINZLER

Lozada, B. B., and Furman, B.: Chagas' Heart Disease (New Electrocardiographic Pictures). Medicina **14:** 71 (Apr.), 1954.

Nine patients out of 35 with Chagas' heart disease showed two new electrocardiographic patterns. In seven cases, an electrocardiographic picture of infarct was seen which was characterized by QRS complexes in the chest leads without the evolutive changes in T wave, typical of arteriosclerotic infarct. Its occurrence, (20 per cent) places this pattern in third place in this disease, after extrasystoles and bundle-branch block. Anatomic examination did not show new or old infarcts, but did reveal fibrillar and interstitial myocarditis.

In three patients out of the group of nine, frequent outbursts of paroxysmal tachycardia resistant to quinidine, procaine, potassium, etc., were seen. Stokes-Adams syndrome associated with very high heart rate was present in two cases, and the authors suppose that ventricular flutter or fibrillation might have been the immediate cause of death. That belief prompted the chronic treatment with antifibrillatory drugs and abstention from digitalis in these types of cases.

RONCARONI

Cossio, P., Mosso, H. E., Berreta, J. A., and Fustinoni, O.: The Ballistocardiogram in Lutembacher Syndrome. Medicina **14:** 101 (Apr.), 1954.

Ballistocardiograms were taken in eight patients, six of them with Lutembacher syndrome and two with atrial septal defect. Diagnosis was established clinically and supported by catheterization. In all cases the waves were normal or increased in size; the authors attribute this to the high cardiac output found. In pure mitral stenosis, the waves of the ballistocardiogram are small. The authors believe, then, that in cases of mitral stenosis in which increased ballistocardiographic waves are seen, the association with atrial septal defect is most probable.

RONCARONI

Friese, G.: The Significance of the Ta wave in Electrocardiographic Diagnosis. Ztschr. Kreislaufforsch. **43:** 159 (Mar.), 1954.

Examples are presented of various abnormalities of the P-R and S-T segments, and of the QRS deflection, attributable to superposition of a Ta wave. Of practical importance is an apparent depression of S-T in the limb leads following exercise, when, with acceleration of the rate, the Ta wave becomes more pronounced. In the precordial leads, where the auricular deflections are normally smaller, this usually does not occur, and for this reason the routine use of chest leads in an exercise tolerance test is advocated.

PICK

Bayley, R. H., and Conrad, C. L.: The Zero Potential of the Electrical Field Produced by the Heart Beat. Circulation Research **2:** 104 (Mar.), 1954.

Eighteen human subjects seated within a spherical integrating electrode were immersed in a homogeneous tap-water conducting medium. The zero of potential of the electrical field produced by the heart beat, by which the potential function on remote electrodes may be evaluated, was defined and measured by the average value of the potential over the surface of the large integrating electrode. The zero of potential thus defined was apparently free of assumptions of any kind and was used to evaluate the potential variations of the three-branch and four-branch Wilson central terminal.

A comparison of the potential variations of V_{T_3}, the three-arm terminal with equal resistances, with those of V_{T_4}, the four-arm terminal with equal resistances, indicates that unless unequal resistances are used in the latter the former is best suited for recording the (O → y) and the (O → z) components of the spatial vectorcardiogram. The three-branch Wilson terminal was found to have a satisfactory zero of potential in 4 of the 18 subjects. Equations were presented to show the potential functions for a nonhomogeneous spherical conducting medium with centric dipole.

MAXWELL

McKusick, V. A.: The Effect of Lithium on the Electrocardiogram of Animals and Relation of this Effect to the Ratio of the Intracellular and Extracellular Concentrations of Potassium. J Clin. Invest. **33:** 598 (Apr.), 1954.

When the serum lithium concentration is elevated, there are electrocardiographic changes which are indistinguishable from those of hyperkalemia. Lithium causes an elevation of serum potassium, probably through a direct displacement from the intracellular site. The author suggests that the electrocardiographic changes found in hyperlithemia may be secondary to changes in the ratio of intra- to extracellular potassium, but this does not exclude the possibility of a direct action of lithium in the production of electrocardiographic changes.

WAIFE

Kittle, C. F., Reissmann, K. R., Dimond, E. G., and Schafer, P. W.: Torsion Ballistocardiography in Cardiovascular Surgical Patients. J. Thoracic Surg. **27:** 107 (Feb.), 1954.

Using a torsion ballistocardiograph, the authors studied subjects with various types of acquired and congenital heart disease before and after operation. The tracings obtained from patients with mitral stenosis were consistently abnormal, a marked diminution in the entire ventricular complex being found, with comparative increase in the diastolic components. Following valvulotomy, the initial waves increased markedly in amplitude and no delay was seen in their onset. At the same time the diastolic waves became proportionally smaller. In patients with coarctation of the aorta the abnormalities in the ballistocardiogram consisted of major changes in the K wave and minor alterations in other complexes. These were reversed in varying degrees after operation. In the presence of a persistent ductus arteriosus, a strong positive wave was noted at the end of systole which disappeared after operation. In patients with chronic constrictive pericarditis, unusually large diastolic waves were found. Following pericardiectomy, there was a gradual reversion of the abnormal ballistocardiogram to a normal one.

ABRAMSON

ENDOCRINE EFFECTS ON CIRCULATION

Soffer, L. J., Elster, S. K., and Hamerman, D. J.: Treatment of Acute Disseminated Lupus Erythematosus with Corticotropin and Cortisone. Arch. Int. Med. **93:** 503 (Apr.), 1954.

Thirty-two patients with acute disseminated lupus erythematosus were treated with cortisone or corticotropin. This series includes 26 females and 6 males. Their ages vary from 11 to 60 years, but the greatest incidence of the disease occurred during the second, third, and fourth decades. Of the 32 patients, 23 are living and reasonably well and 9 have died. Of the 23 who are living, 8 are in a state of remission without treatment, thus far lasting from 2 to 30 months. The remaining 15 patients require continued hormonal therapy on a maintenance basis. Of the nine patients who died, six succumbed to progressive renal failure, one to status epilepticus, one to a disseminated fungus infection, and one to inadequate therapy.

Typical L.E. cells were demonstrated in the peripheral blood in all members of the series, and the sedimentation rate was found to be elevated in 90 per cent of the group. Slightly more than half the patients had evidence of renal disease, and a third showed a definite elevation of the blood urea nitrogen. More than a third of the group had falsely positive serologic tests for syphilis. The lupus cells persisted during hormone-induced remission, although they were much reduced in number and more difficult to find. The remaining clinical and laboratory manifestations improved in varying degrees. The complications resulting from treatment with cortisone or corticotropin are discussed. Almost all of the patients developed some evidence of hypercorticalism. Hypertension, edema, congestive heart failure, psychiatric abnormalities, convulsions, and alkalosis occurred with a greater degree of frequency in the patients who died than in those who are living. The side-effects of hormonal therapy are generally reversible when the dosage is reduced or treatment is entirely discontinued.

BERNSTEIN

Grollman, Arthur: Effect of Cortisone on Serum Calcium, Magnesium, and Phosphate Levels in Nephrectomized Dogs. Proc. Soc. Exp. Biol. & Med. **85:** 522 (Apr.), 1954.

Five nephrectomized dogs were maintained on a dietary regimen high in calories, free from protein and electrolytes. The daily water loss from insensible perspiration was replaced. Calcium, phosphate, and magnesium levels were followed during the experiment. Cortisone (5 mg. per kilogram of body weight per day) was given after an unspeci-

fi l control period. In each instance serum calcium le els rose 4 mg. per 100 cc. to 6 mg. per 100 cc. al ove the control valves. Phosphate and magnesi m levels rose concomitantly. When cortisone w s discontinued the levels of calcium fell. Phospl orus and magnesium levels were not measured. N clinical observations on the dogs are reported. T e author urges caution in use of cortisone in pati nts with impaired renal function because of the h percalcemia which develops and possible "toxic" ef ects therefrom.

HARVEY

Hoover, M. P., and Manning, G. W.: The Effects of Cortisone and ACTH on Artificially Induced Cardiac Infarction in the Dog. Am. Heart J. **47:** 343 (Mar.), 1954.

Three groups of experiments were carried out: (1) to determine the effect of cortisone on infarct healing, (2) to determine the effect of corticotropin on infarct healing, and (3) to determine the effect of corticotropin and cortisone on mortality following sudden ligation of the left circumflex in the conscious dog. The method of operative procedure was such that the ligature was tightened and the artery occluded 10 days following operation, during which time the ligature was placed loosely about the artery. The animals were studied for 21 days after ligation and then sacrificed for pathologic studies. The results indicated that corticotropin and cortisone have little or no effect on the healing of experimentally produced cardiac infarction, and the use of these substances does not influence in any way the immediate mortality following sudden coronary occlusion in the conscious dog.

RINZLER

Lubetscher, F.: The Effect of Adrenalin and Nor-Adrenalin on the Circulation under Stress. Ztschr. Kreislaufforsch. **43:** 90 (Feb.), 1954.

The response to exercise was studied in 15 normal persons subsequent to injection of epinephrine (15 mg. per kilogram) and norepinephrine (same dose). The pulse rate and blood pressure responded in the usual normal way except for minor variations of pressure and less tachycardia following norepinephrine. The electrocardiogram following exercise showed no abnormalities in contour, but in the majority of cases it showed a disturbance of impulse formation or conduction.

PICK

Blanc, W., and Fabre, J.: The Effect of Cortisone on Experimental Allergic Myocarditis. Helvt. med. acta **21:** 88 (Fasc. 1), 1954.

Two injections of horse serum given at 12-day intervals cause allergic myocarditis in rabbits. This myocarditis is characterized by perivascular and interstitial leukocyte infiltrates, and by lesions of the collagen substance and the muscular fibres. In addition, there is deformation of the valvules.

In the case of animals treated with cortisone, at the rate of 4 mg. per kilogram of body weight daily, the inflammatory signs are practically nonexistent. On the other hand, the lesions to the muscular system and the collagen substance are hardly affected.

The anti-inflammatory effect of cortisone likewise makes itself felt when that hormone is administered before the first sensitizing injection, or even on the day preceding the second injection of serum. It cannot be accounted for in terms of a reduced formation of antibodies, nor yet of the elimination of the antigenic conflict, but rather in terms of the direct influence of cortisone upon the vasular permeability of the myocardium and on the proliferation of histiocytes.

AUTHORS

HYPERTENSION

Henkes, H. E., and van der Kam, J. P.: Electroretinographic Studies in General Arterial Hypertension and in Arteriosclerosis. Angiology **5:** 49 (Apr.), 1954.

Fifteen patients suffering from systemic arterial hypertension were examined electroretinographically and compared with another group of 15 patients showing general arteriosclerosis without hypertension. All demonstrated a normal ophthalmoscopic picture. However, in the majority of cases a pathologic electrical response was recorded. In the hypertensive series the supernormal b-potentials were predominant; this finding was considered to represent a heightened irritability of the retinal neurones. In the patients with arteriosclerosis, there was a subnormal response, ascribed to an insufficient oxygen supply of the retinal neurones.

ABRAMSON

Heptinstall, R. H.: Renal Biopsies in Hypertension. Brit. Heart J. **16:** 133 (Apr.), 1954.

Renal biopsies were studied from 50 individuals undergoing sympathectomy for hypertension. The vascular changes are representative of the changes of the kidney as a whole, except for instances of pyelonephritis and of malignant hypertension. In 30 individuals with hypertension, the renal biopsies showed minimal vascular changes. The drop in blood pressure following operation was not dependent upon the degree of vascular involvement. Drops in blood pressure were obtained equally well with a limited type of sympathectomy.

SOLOFF

Walker, G., Levy, L., Hyman, A., and Romney, R.: Prolonged Hypotensive Reaction to Hexamethonium. J. A. M. A. **154:** 1079 (Mar. 27), 1954.

The authors present three cases that will em-

phasize the prolonged hypotensive reactions which may result from the oral administration of hexamethonium compound. Such mechanisms are as follows: (1) An increased degree of absorption might occur as a result of constipation. Constipation would tend to be perpetuated by the continuing effects of the absorbed hexamethonium. An increase in amount of drug may also occur during compensation from congestive heart failure when edema of the intestinal wall subsides and absorption is increased. (2) Decreased renal excretion would tend to cause higher blood levels of hexamethonium. The hypotensive reaction following initial impairment of renal filtration would result in a fall of blood pressure and a further diminution in filtration. (3) Excessive dosage may cause trouble. It is essential in the proper management of patients who are taking hexamethonium that proper emphasis be placed on repeated regular medical care, the report of any untoward symptoms, and discontinuance of therapy with the drug if any symptoms suggesting marked hypotension appear, or if constipation occurs.

KITCHELL

Smirk, F. H.: Results of Methonium Treatment of Hypertensive Patients, Based on 250 Cases Treated for Periods up to Three and One-half Years, Including 28 with Malignant Hypertension. Brit. M. J. **1:** 717, (Mar. 27), 1954.

The results in the cases of malignant hypertension were undisputably excellent. Seven of the 28 patients in the group died; many of the surviving patients were returned to a productive existence. Results in the benign hypertension groups showed improvement in enough parameters to convince one that the therapeutic program has been of benefit. A few patients were treated with hexamethonium by mouth; others were given three daily injections of the aqueous solution. Subsequently P.V.P. was used as a vehicle to slow absorption and ephedrine was added for the same reason. A new methonium compound (M. & B. 2050A) was employed in the latter part of the study with improved results. The new agent can be administered by mouth. The reasons for poor results are discussed.

MCKUSICK

Schaffer, A. J., and Markowitz, M.: Hypertension Treated by Nephrectomy: A Report of Four Additional Cases and a Reevaluation of Prognosis and Criteria for Operation. Am. J. M. Sc. **227:** 417 (Apr.), 1954.

From an analysis of the literature, the authors found that unilateral nephrectomy for removal of a diseased kidney resulted in correction of hypertension in 28 of 30 children treated in this fashion. Four of these case histories are in the present report. It is stated that more than one third of the patients of all ages with unilateral kidney disease will be rendered normotensive by nephrectomy, more than one third will be unimproved and the remainder improved. Although children respond more favorably to the operation, advanced age or long duration of hypertension does not contraindicate this type of therapeutic approach. Furthermore, the absence or presence of retinopathy has little bearing on the outcome. Several criteria for the selection of patients for the operation are listed. The only valid contraindication for unilateral nephrectomy appears to be infection or diminution of function of more than minimal degree of the presumably normal kidney.

SHUMAN

Muirhead, E. E.: Experimental Hypertension Following Bilateral Nephrectomy. South. M. J. **47:** 110 (Feb.), 1954.

A relatively "low" sodium intake (48 to 144 mEq.) after bilateral nephrectomy of the dog was associated with an incidence of significant hypertension (36 per cent) which was no greater than that previously encountered following renal ablation, no water or salt intake and no salt depletion. A relatively "high" protein intake (about 3 Gm. per kilogram per day) alone was not associated with hypertension after renal ablation. It is suggested that the "uremia" and periodic vomiting may have deterred the expression of hypertension.

A "high" sodium intake (270 to 420 mEq.) given intravenously as a concentrated solution (2.5 per cent sodium chloride) aggravated the hypertensive cardiovascular disease of bilateral nephrectomy. A relatively high protein intake plus a low sodium intake, with and without dialysis, consistently aggravated the hypertensive state following nephrectomy.

BERNSTEIN

Wilson, C.: Renal Factors in Hypertension. Lancet **2:** 579, 632 (Sept. 19, Sept. 26), 1953.

The subject is discussed under three main headings: (1) investigation of possible humoral pressor substances of renal origin; (2) studies of the course of hypertension in animals by modifications and extensions of Goldblatt's experiment; and (3) the relationship of anatomic lesions of the kidney to hypertension.

It is pointed out that the relationship of the renin system to chronic hypertension in man is dubious or at the best obscure. It may, however, have some role in shock and in the physiologic responses to fall in blood pressure.

The rat is championed as a useful experimental animal, since it resembles man in its hypertensive responses much more closely than do the dog and rabbit, for instance. Partial occlusion of one renal artery causes persistent hypertension. Encephalopathy often develops without uremia and is relieved by removal of the ischemic kidney. Vascular lesions

like malignant hypertension occur in the ipsilateral non-ischemic kidney. Hypertension is often sustained for long periods without evidence of vascular damage.

In connection with the question of whether there is a difference in mechanism of acute and chronic experimental hypertension, it has been suggested in the past that extrarenal, possibly neurogenic, factors may be responsible for the maintenance of blood pressure after removal of the ischemic kidney. The author quotes the important demonstration of Byrom and Dodson (1949) that the persistence of hypertension is due to changes in the contralateral non-ischemic kidney and therefore that the chronic hypertension is, like the acute hypertension, of renal origin.

It is now clear that total nephrectomy is followed by hypertension, so-called renoprival hypertension. This is strong evidence for extrarenal factors. The blood pressure takes about three days to attain unequivocally elevated levels after bilateral nephrectomy. The removal of the clot from the renal artery of an ischemic kidney with the other kidney removed results in return of the blood pressure to normal levels in less than 12 hours. If renal and renoprival hypertension have different mechanisms, excision of a sole ischemic kidney should be followed by a biphasic response, with early rapid fall of blood pressure to normal and return of hypertension three to four days later. This is not the case; hypertension continues unabated suggesting that the extrarenal factor is already operating in the hypertension of renal artery constriction.

An experimental preparation useful in the study of the problem under consideration here is that of parabiotic rats. These animals, litter mates joined in the scapula area three weeks after birth, remain healthy and active as long as two years. The rate of circulatory exchange has been found to be about 1 per cent of the blood volume per minute.

The presence of adrenal-gland tissue is essential for the development of both renal and renoprival hypertension. There are experimental results suggesting either that the adrenals in the hypertensive rat are overactive or that their secretions are accumulating through the failure of some renal inactivating mechanism.

The lesions in the contralateral kidney in cases of one ischemic kidney are quite clearly due to the hypertension itself and not to pyelonephritis in the experimental animals or to renal failure as has been proposed as alternative possibilities.

The vicious cycle concept explains the chronic hypertension without demonstrable renal failure, which often ends in malignant hypertension, following type 1 nephritis. Unilateral renal disease with hypertension has a very direct parallel in the disease produced in rats, and there is adequate explanation, too, for the fixation of hypertension which may occur, making results of nephrectomy less than fully successful.

The work of Byrom, involving introduction of transparent windows into the calvarium of rats, convincingly demonstrates cerebral arterial spasm during hypertensive encephalopathy. General cerebral edema was a late development.

McKusick

Walker, A. E., Browne, K. M., McQueen, J. D.: Effect of Hypothalamic Lesions on Canine Neurogenic Arterial Hypertension. Proc. Soc. Exp. Biol. & Med. **85**: 474 (Mar.), 1954.

Twenty-four dogs were made hypertensive by bilateral resection of the carotid sinus, sectioning of the vagosympathetic trunk on one side, and sectioning of the aortic depressor nerve on the other side. Measurements of blood pressure were made by percutaneous puncture of the femoral artery. After hypertension was well established (6 to 20 months), hypothalamic lesions were produced electrically by a coagulating current passed through electrodes inserted into the desired region through burr holes and positioned by fluoroscopic control. After varying times animals were sacrificed and careful microscopic examinations performed of all tissues. Fourteen dogs survived the surgical procedures and lived long enough for study. No lesion produced in the hypothalamus by this electrocautery technic caused a fall in arterial hypertension. Thus, the activity of medullary cardiovascular centers, heightened when released from peripheral inhibition, is not permanently influenced by hypothalamic lesions.

Harvey

Finnerty, F. A.: Does Vascular Damage Follow Toxemia of Pregnancy? J. A. M. A. **154**: 1075 (Mar. 27), 1954.

Although 95 per cent of 303 patients who were referred to a toxemia clinic run in conjunction with the obstetric department at Gallinger Municipal Hospital were referred as toxemia cases, only 45 of this group were diagnosed as true toxemia. One hundred forty-nine of the hypertensive group remained hypertensive during pregnancy. Sixty-seven patients became normotensive during pregnancy and hypertensive again immediately after delivery. Two patients in the group who had hypertensive vascular disease plus superimposed toxemia showed grade I hypertensive retinopathy prior to the toxemic episode and grade II retinopathy six weeks postpartum. All the patients with true toxemia showed a generalized retinal sheen. Although not a specific finding for toxemia, its importance lies in the fact that it is not seen in uncomplicated hypertensive vascular disease. Retinal sheen is described as a wet glistening appearance similar to many reflections of light on a wet street at night. The author points out that the presence of definite

hypertensive retinopathy in the absence ofnal reti sheen in a pregnant patient with elevated blood pressure should be reassuring to the physician; these patients are not toxemic. They are patients with hypertensive vascular disease who happen to be pregnant. Examination of the retinas of 25 of the true toxemic group six weeks postpartum revealed no abnormalities. In 20 patients, however, despite return of blood pressure to normal and disappearance of edema and albuminuria, examination revealed definite retinopathy. These retinal changes are attributed to the duration of the toxemia rather than to its severity.

KITCHELL

PATHOLOGIC PHYSIOLOGY

Enderby, G. E. H.: Postural Ischaemia and Blood Pressure. Lancet **266:** 185 (Jan. 23), 1954.

The author discusses the various factors involved in the production of postural ischemia. He points out that the main mechanism is the hydrostatic effect of gravity on the column of blood above or below the heart. For every 15 inches of vertical height of a site above heart level, there is a reduction in local blood pressure of about 30 mm. Hg. This response can be utilized during surgical procedures to prevent capillary bleeding at the operative site. However, the local blood pressure must be reduced to 35 to 45 mm. Hg to obtain such a situation. For the adequate control of hemorrhage, it is therefore necessary to drop the pressure at heart level to 60 mm. Hg and elevate the portion of the body being subjected to surgical intervention.

ABRAMSON

Harrison, W., and Liebow, A. A.: The Effects of Massive Intravenous Infusions with Special Reference to Pulmonary Congestion and Edema. Yale J. Biol. & Med. **26:** 372 (Apr.), 1954.

Saline solutions were infused into the left atrium and pulmonary artery of dogs, using a method described by the authors. The presence and degree of pulmonary edema were judged according to the ratio of lung weight to body weight. In general, retention of fluid was proportional to the amount of fluid administered, but this relationship was not constant. Pulmonary edema was most apt to occur in those animals which received the most fluid, had the least urinary excretion, and developed the highest blood volume. Nevertheless there were exceptions. The mechanisms responsible for the various excretion rates were not apparent.

One highly important factor in the development of pulmonary edema appeared to be a pulmonary capillary pressure exceeding 20 cm. of water for more than 15 minutes. The rise in pulmonary venous pressure was relatively rapid compared with the concomitant rise in systemic venous pressure. This finding tends to confirm previous suggestions of a relative indistensibility of the pulmonary venous-left atrial segment. The finding of ascites in the absence of subcutaneous edema or even pulmonary edema may be explained on the basis of previously reported steeper increases of portal venous pressure than of systemic venous pressure during massive intravenous infusions.

ENSELBERG

Gitelson, S.: Determination of the Venous Pressure in the Sitting Posture. Brit. Heart J. **16:** 147 (Apr.), 1954.

The antecubital venous pressure is measured in a sitting position by using as a reference point a point 4 cm. below the fourth sternal costal junction, and 1 cm. lower in the supine position. The venous pressure by each method is the same in individuals who have either no heart failure, mild failure or pure left heart failure. In the majority of those with severe right heart failure, the venous pressure is slightly lower in the sitting than in the supine position. However, following treatment there is a proportionate drop in the venous pressure taken in the sitting and supine position. There is a tendency for the venous pressure to remain stable in the hypertensive and arteriosclerotic individuals and in individuals with ascites and hepatic cirrhosis. A venous pressure above 10 cm. is abnormal for the sitting position.

SOLOFF

Scheinberg, P., Blackburn, L. I., Rich, M., and Saslaw, M.: Effects of Vigorous Physical Exercises on Cerebral Circulation and Metabolism. Am. J. Med. **16:** 549 (Apr.), 1954.

Utilizing vigorous physical exercise to produce metabolic acidosis with consequent decrease in arterial blood carbon dioxide content and pH but without significant change in arterial pCO_2, the investigators found that exercise resulted in a decrease in cerebral vascular resistance and an increase in cerebral oxygen consumption. The decrease in mean cerebral blood flow which results from motionless standing did not occur with exercise. There was no change in cerebral respiratory quotient. Although exercise resulted in a striking fall in blood carbon dioxide content and pH, no correlations could be made between these changes and the alterations in cerebral circulatory or metabolic functions. There was a close correlation between changes in cerebral vascular resistance and cerebral oxygen consumption, although the reason for this is not known.

HARRIS

Wood, E. H., Leusen, I. R., Warner, H. R., and Wright, J. L.: Measurement of Pressures by Cardiac Catheters in Man. Minnesota Med. **37:** 87 (Feb.), 1954.

An electromagnetic hydraulic pressure oscillato has been used to study the dynamic response char

act ristics, and a motor-driven cam apparatus to stu y the pressure fluctuations caused by reproducible sine wave and square wave motions of cardiac cat eters connected to strain gauge or capacitance ma ometer systems. These studies were carried out im ediately after use of these identical systems for rec rding of intracardiac pressure pulses during 47 liagnostic cardiac-catheterization procedures in pa ents with various types of cardiovascular abnormalities.

A close correlation was demonstrated between the sus eptibility of cardiac catheter manometer systems to pressure artefacts induced by motion of the catheter outside of the body, and the degree of distortion by artefact of pressure pulses recorded by the same catheter system from the beating heart. Pressure pulses, recorded by conventional catheters threaded through the beating heart, should be regarded with a high index of suspicion, since the lower frequency artefact induced by motion of the catheter synchronous with the heart beat may be of such character and be fused with each pressure pulse in such a manner as to be unrecognizable as artefact.

BERNSTEIN

Sapirstein, L. A., Greene, R. W., Mandel, M. J., and Hull, H. B.: A Constant Infusion Technique for the Determination of Cardiac Output. Am. J. Physiol. **177:** 134 (Apr.), 1954.

Para-aminohippurate was infused constantly into the venous circulation. A direct Fick for cardiac output was determined by analysis of arterial plasma during and after the infusion. Cardiac catheterization is not required and the results agree well with determinations made by the single-injection dye-dilution method.

OPPENHEIMER

Nordenstrom, B.: Pulmonary Circulation Time. A Densometric Study. Acta radiol. **41:** 209 (Mar.), 1954.

Sudden stoppage of the circulation through one lung, such as after pneumonectomy or during temporary occlusion of a pulmonary artery, will result in as much blood flow through the contralateral lung per unit of time as formerly had passed through both lungs combined. This requires either a doubling of blood flow through the remaining lung, or a decrease in circulating time to one half of the preocclusive value, or a combination of the two.

The author has adapted a densometric procedure to study this problem and presents the findings in six dogs. The circulation time was shorter when one pulmonary artery was occluded than when there was unobstructive circulation through both lungs. The experiments provide evidence suggesting that the pulmonary circulation adapts itself to occlusion of the pulmonary artery to one lung through augmentation of blood volume circulating through the contralateral lung.

SCHWEDEL

Remington, J. W.: The Relation Between the Stroke Volume and the Pulse Pressure. Minnesota Med. **37:** 105 (Feb.), 1954.

A critical analysis of factors bearing on the pulse contour method for determinating stroke volume is presented. These include the factor of nonlinear volume-pressure characteristics of the aorta, the action of the smooth musculature of the aorta in producing intraindividual variability in pressure-volume relationships, variability in the dimensions of the elastic chamber (arterial tree) which is receiving the output of the ventricle, and others. In some 400 comparisons (in dogs) of stroke volume by the Fick method with that by the pulse contour method, 73 per cent of the observations were found to lie within the limits of ±20 per cent. Finally the author returns to a consideration of the topic indicated by the title and presents a table which can be employed for the prediction of the stroke volume per square meter of body surface area. This very approximate method makes use of the brachial arterial pressure determined with the clinical cuff and is stated by the author to have an average error of about 25 per cent.

MCKUSICK

Calazel, P., Cassagneau, J., Esclavinat, M., Bollinelli, R., Ducuing, J., and Meriel, P.: A Study of Coronary Flow. 1. First Results in the Normal Human. Arch. mal. coeur **47:** 289 (Apr.), 1954.

The dynamics of the coronary circulation were studied by the method of Bing in eight individuals with normal hearts. The technic is described in detail and some limitations and necessary corrections of the results obtained are pointed out.

In the normal, the oxygen content of coronary venous blood varies from case to case but is always lower than 6.6 volumes per cent. It varies with the arterial oxygen. Coronary blood flow varies within a considerable range and seems to depend on the age, the weight of the heart and body surface. The oxygen extraction by the heart that is the difference between oxygen saturation of coronary arterial and venous bloods is, however, constant. Oxygen extraction, under physiologic conditions, is high and maximal so that increased metabolic requirements, for example during exercise, can be met only by an increase in coronary flow. Determination of coronary flow is possible in any laboratory equipped for hemodynamic studies. In the experience of the authors, catheterization of the coronary sinus was successful in 72 per cent of all attempts without accidents. The procedure is, however, a long and tiresome one for the patient. Determination of the coronary flow permits a clarification of some prob-

lems of the dynamics of coronary circulation, of cardiac metabolism, and of energetic reserves of the heart under physiologic and pathologic conditions.

PICK

Evans, W., Swann, P.: Lone Auricular Fibrillation. Brit. Heart J. **16:** 189 (Apr.), 1954.

Twenty instances of auricular fibrillation without demonstrable heart disease are described. All of these individuals were males and in the older age group. This arrhythmia is usually present without any symptoms and is discovered accidentally during a routine examination. The heart rate is rarely above 90 per minute. The heart size is normal and the electrocardiogram shows no axis deviation. The prognosis is excellent. Treatment is not necessary unless activity of a degree sufficient to increase the heart rate unduly is necessary for the individual. Under such circumstances, digitalization is advised.

SOLOFF

Nahasone, N., Watkins, E., Janeway, C. A., and Gross, R. E.: Experimental Studies of Circulatory Derangement Following the Massive Transfusion of Citrated Blood. J. Lab. and Clinical Med. **43:** 184 (Feb.), 1954.

A series of experiments performed in dogs is presented to study the derangements in circulatory dynamics caused by infusion of amounts of citrate solution comparable to those used in human beings under present day transfusion procedures. Electrocardiograms, arterial pressures, and pulse contours were obtained; stroke volume index and total peripheral resistance were calculated in normal anesthetized dogs and in dogs subjected to infusions of citrate solutions and citrated blood in varying amounts at varying rates both intravenously and intra-arterially. If large amounts of citrate solution or citrated whole blood are infused at constant rates a picture of hypocalmenia develops with a typical electrocardiographic pattern, and circulatory collapse occurs. This process was prevented or reversed with concomitant administration of calcium chloride. Blood rendered noncoagulable by passage over a resin column of a polyvinyl plastic is also made deficient in bivalent cations. Preliminary experiments suggest that such blood, though deficient in bivalent cations, can be administered in great amounts without the same deleterious effect on circulatory dynamics as citrated blood, for this blood has no excessive ion binding substance as citrated blood has, and, therefore, the rapid transfer mechanisms which take place are sufficient to maintain serum concentration.

HARVEY

Schaeffer, R. D., and Little, R. C.: The First Heart Sound in Ventricular Contractions Arising from the Apex and Base. Proc. Soc. Exp. Biol. & Med. **85:** 639 (Apr.), 1954.

Studies were done on the exposed hearts of five anesthetized dogs to determine the time delay between the onset of electrical activity associated with ventricular contraction and the production of the sound thought to be that of closure of the A-V valves. Simultaneous electrocardiographs and phonocardiographs were recorded with normal beats and with ventricular contractions produced by a suitable electrical stimulation either at the apex or base of the right ventricle after a tetanizing current had been applied to the right vagus. It was found that this interval, called the heart sound time for normal beats, was 0.048 second, for apical ventricular contractions 0.080 second, and for basal ventricular contractions 0.093 seconds. Statistically this evidence is sound for the P value of these comparisons is less than 0.1 per cent. Heart sound times were determined on four humans with ectopic ventricular contractions by phonocardiography. The same pattern of delay occurred in these records, but the timing was slightly longer for basal ventricular contractions (0.121 seconds). Again the P value was less than 0.1 per cent in these comparisons.

HARVEY

Adams-Ray, J., Hagberg, S., Hjelmström, P., and Olsson, S. E.: A Roentgen Stereophotogrammetric Method for Measurement of Variations in the Volume of Organs in Living Animals. Angiology **5:** 59 (Apr.), 1954.

The authors describe a method of studying variations in the volume of the liver in laboratory animals by means of a roentgen stereophotogrammetric procedure. The animal is operated on and pieces of metal are fixed in its liver in such a way that a polyeder is obtained, the metal objects constituting its corners. Steroscopic roentgenograms are then taken by simultaneously releasing two x-ray tubes with known position in relation to the film. This produces a double reproduction of each piece of metal. The configuration in space of the pieces of metal is determined by measuring the image co-ordinates and by knowing the position of the x-ray tubes. The volume of the polyeder of reference is then computed from the co-ordinates of the metal pieces. Variations in volume between successive exposures can be directly determined from variations in the co-ordinate computations between different x-ray photographs.

ABRAMSON

Horvath, S. M., and MacCanon, D. M.: Variations in Pulmonary Vascular Pressures. J. Thoracic Surg. **27:** 204 (Feb.), 1954.

Using nine anesthetized dogs, the authors measured pressures in the left atrium, pulmonary vein and "pulmonary capillary." The latter was obtained by wedging a catheter into a suitable pulmonary artery. It is pointed out that pulmonary capillary

pressures might, under certain circumstances, represent pulmonary capillary venule pressures.

ABRAMSON

Gr[illegible]etz, D., Corsa, L., Jr., Cook, C. D., Keitel, [illegible]. G., and Talbot, N. B.: Measurement of Total [illegible]ody Exchangeable Potassium and Erythrocyte [illegible]otassium in Nephrotic Children. J. Clin. Invest. **33**: 680 (Apr.), 1954.

The cellular potassium status of children with nephrotic syndrome was studied by measurement of total body exchangeable potassium via isotope dilution technics and by the determination of the potassium content of the red cells by direct analysis. The evidence indicates that the total body exchangeable potassium, although low in relation to the total edematous body weight, is within normal limits when related to the weight in the absence of edema. It also is normal in relation to height and urinary creatinine output. Similarly, normal values were found in the red cell potassium level.

These studies suggest that nephrotic patients may accumulate large amounts of edema without undergoing a major change in the cellular potassium status. Balance data indicate little or no change in potassium shifts despite large shifts in sodium balance.

WAIFE

Filley, G. F., Gay, E., and Wright, G. W.: The Accuracy of Direct Determinations of Oxygen and Carbon Dioxide Tensions in Human Blood in Vitro. J. Clin. Invest. **33**: 510 (Apr.), 1954.

The authors report two modifications of the original Riley bubble method for the direct determination of blood-gas tensions. These modifications reduce the dependence on technical skill and lead to greater precision. The details are given in the article.

WAIFE

Hackel, D. B., Goodale, W. T., and Kleinerman, J.: Effects of Hypoxia on the Myocardial Metabbolism of Intact Dogs. Circulation Research **2**: 169 (Mar.), 1954.

By catheterizing the pulmonary artery, a systemic artery and the coronary sinus, it was possible to study the myocardial metabolism of intact, anesthetized dogs during different degrees of hypoxia. Total left ventricular oxygen consumption was maintained during administration of 10 per cent and 5 per cent oxygen, owing to increase in coronary flow and myocardial oxygen extraction. The administration of 10 per cent oxygen resulted in little change in the carbohydrate uptake by the heart. Five per cent oxygen resulted in increased arterial levels of lactate and pyruvate, and significantly decreased arteriovenous differences and coefficients of extraction of pyruvate, lactate and glucose. At the same time, the total utilization of these substances was maintained. Complete oxygen deprivation resulted in negative arteriovenous differences for lactate, and markedly decreased or negative values for pyruvate.

MAXWELL

Nylin, G.: Circulatory Studies with Radio-Active Isotopes. Acta med. scandinav. **147**: 275 (fasc. 4), 1953.

The various studies of the circulation with radioactive materials are reviewed in detail. It is pointed out that radioactive phosphorus permeates the corpuscles slowly and leaves them relatively slowly, whereas plasma is labeled quickly and gives up its phosphorus easily to the various tissues to be excreted finally in the urine. The discrepancies between methods of measurement of circulating blood volume and mixing conditions within the body by use of blue-azo-dye technics and those employing radioactive phosphorus are discussed. The rapid dispersion of the dyes from the blood into the tissues is felt to decrease the accuracy of methods employing these substances. Nylin and his associates have found the average normal amount of red blood corpuscles to be 31 Gm. per kilogram of body weight, although the range of normal variations is wide.

Dilution curves following intravenous injection of labeled blood corpuscles disclose active blood corpuscles in the arterial blood after five to six seconds, with a maximum occurring 12 seconds after injection and a minimum recorded in 20 seconds. A second peak, representing recirculation, occurs at 30 seconds. In a patient with an extremely dilated heart, labeled corpuscles appeared in the arterial blood one-half minute after injection, reached a maximum in 50 seconds and fell to a minimum in 90 seconds. In this patient the total blood volume was about 3,000 cc. greater than normal, and a large fraction of this was believed to be stored in the heart as an enormous residual quantity of blood. Studies of the behavior of the spleen with labeled blood corpuscles showed that man, unlike the dogs observed by Barcroft, showed no store of blood in that organ, which was discharged after muscular exercise, nor after the injection of epinephrine.

By this technic it was found that over 600 cc. of blood can be isolated in the lower legs by means of blood pressure cuffs. Various observations have been made in the study of shock. It has been found that during some operative procedures, mixing of blood does not occur normally nor as quickly as under normal circumstances.

Isotopes other than radioactive phosphorus have been studied. An ideal radioactive material should have the following characteristics: (1) it should always be ready for use and should not lose activity, for at least one year; (2) radiation must be easily measurable; (3) the indicator should adhere firmly in the blood corpuscles; (4) the half-time of the indicator should be long enough to make measure-

ments easy to carry out but preferably shorter than one day; and (5) it is desirable that no centrifuging of the blood samples should be necessary. A new indicator which has been studied is radioactive potassium chloride. Radioactive K^{42} has the advantage of a half-time of only 12 hours, and it remains in the corpuscles for a longer time than does phosphorus. Radioactive thorium has a short half-time and also accumulates in the blood corpuscles up to 99 per cent, so that the activity of the plasma need not be considered and the blood need not be centrifuged, but before or after injection it may be measured directly in "Zerahn" cuvettes.

ROSENBAUM

PATHOLOGY

Lasky, I.: Massive Dystrophic Calcification of the Myocardium. Ann. Int. Med. 40: 626 (Mar.), 1954.

Dystrophic calcification is the term applied to the laying down of calcium in dead, degenerated or devitalized tissue. As it applies to the heart it can include: (1) pericardial calcification, which is generally the end result of previous inflammation; (2) valvular calcification, as a result of previous damage to the mitral, aortic or tricuspid valve; (3) calcification of the mitral annulus fibrosis; (4) coronary artery calcification; (5) myocardial calcification; and (6) endocardial calcification. The most common is the calcification which results from previous myocardial infarction and is not associated with abnormalities of calcium or phosphorus metabolism, per se. This type of calcification can thus occur without changes in the circulating blood calcium content. Dystrophic calcification has been related to the low production of carbon dioxide and the slow metabolizing tissue which permits the development of a local zone of alkalinity and, consequently, reduction of calcium solubility. This phenomenon becomes more marked and more extensive in the presence of metabolic upsets such as occur in an area of infarction. On the contrary, metastatic calcification is associated with increased availability of calcium. This type of mineralization is thus found in bone destructive lesions, with hyperparathyroidism and hypervitaminosis D and with renal insufficiency. Massive calcification in myocardial infarcts is relatively uncommon. Although there are not more than 21 undoubted cases in the medical literature to date, the condition occurs in a well-defined group of patients with a characteristic clinical picture and may be demonstrated by standard radiologic technics. The diagnosis is of some prognostic import since these patients, like others with coronary heart disease, are prone to sudden death. Among the 21 cases reported in the literature, the shortest duration between infarction and the discovery of myocardial calcification was approximately six years. In the case described in this report, the primary myocardial insult occurred approximately 21 years previous to the finding of the calcification, and the electrocardiogram showed changes corresponding to the area of myocardial damage and calcification, the changes being diagnostic of a previous myocardial infarction involving the anterolateral portion of the left ventricle. There was no evidence of myocardial failure and the area of calcification, measuring 5 by 7 cm. was demonstrable in the fluoroscope and teleoroentgenogram. Laminagraphic studies of the heart defined the position of the calcification at the level of the left ventricle approximately midway between the anterior and posterior diameter of the mediastinum.

WENDKOS

Coraboeuf, E., and Weidmann, S.: Temperature Effects on the Electrical Activity of Purkinje Fibres. Helvet. physiol. et pharmacol. acta. **12:** 32 (Fasc. 1), 1954.

Membrane potentials of single Purkinje fibers (calf, sheep) were recorded with an intracellular microelectrode, at temperatures between 10 C. and 45 C.

The value of the resting potential (94 mV at 38 C.) and that of the reversed potential difference during activity (35 mV at 38 C.) did not change appreciably when the temperature was varied between 40 C. and 25 C. Outside these limits both the resting potential and the "overshoot" decreased.

In pacemaker regions the threshold potential for spontaneous firing stayed constant (60 mV) over a temperature range of 40 C. to 25 C.

Temperature changes had no marked effect on the shape of the action potential but greatly affected its duration. With spontaneously active preparations the slopes of the different phases had the following Q_{10}-values: upstroke 1.7, descending limb of the initial spike 1.9, plateau 4.5, final repolarization 2.6, slow diastolic depolarization 6.2.

The axoplasm resistance and the membrane direct current resistance increased on cooling, both with a Q_{10} of 1.5.

The findings are discussed on the ground of the "ionic theory of electrical activity."

AUTHORS

Vickers, J. E.: Case of Bullet in Heart with Recovery. A Thirty Year Follow-Up. Am. J. Roentgenol. 71: 89 (Jan.), 1954.

The author presents a case report of a self-inflected bullet into the heart in a man aged 59 who lived thirty years and then died of uremia secondary to benign prostatic hypertrophy. At autopsy the bullet was found in the posterior part of the interventricular septum. The heart chambers were only slightly dilated.

SCHWEDEL

PHARMACOLOGY

Hoffman-Credner, D., and Siedeck, H.: Circulatory-dynamic Alterations Subsequent to Acute and Chronic Use of Hydrazinophthalazine Preparations. Ztschr. Kreislaufforsch. **43:** 217 (Apr.), 1954.

The authors report studies on the effect of intravenous and oral application of Apresoline and Nepresol (1,4-hydrazinophthalazine) in 112 hypertensive patients.

After intravenous injection of 40 mg. Apresoline, cardiac output and minute volume increased, while pulse rate, pulse velocity, mean arterial pressure, amplitude and venous pressure decreased. Similar effects were observed on long-term oral administration of the drug. Side effects consisting of headache, nausea, vomiting and tendency to collapse occurred frequently on both types of application.

Oral Nepresol (25 mg. daily, increasing to 150 mg.) was tolerated without side effects. It had the typical effects of a ganglionic blocking agent, but cardiac output and minute volume rose only after a period of about 30 days.

It is concluded that the clinical use of Hydrazinophthalazine is justified in malignant hypertension. In other types of hypertension it must be used judiciously because of the danger of ischemic reactions, among which impairment of cerebral circulation may endanger the life of the patient.

PICK

Lasch, F.: The Influence of Hydergine Application on Renal Disease. Cardiologia **24:** 155 (Fasc. 3), 1954.

In 61 subjects, including normals, patients with essential hypertension and patients with various types of kidney disease, the effect of prolonged treatment with Hydergine upon renal function was studied and the results submitted to statistical analysis. In about one-half of the experiments a distinct increase occurred in the para-aminohippurate clearances which was statistically significant in a number of cases. This was associated with a marked reduction of blood pressure. Hydergine had no effect on glomerular filtration, filtration rate, and rate of reabsorption.

The results of these experiments suggest that Hydergine increases renal blood flow. This may explain the beneficial effect of the drug observed in patients with acute glomerulonephritis.

PICK

Fistner, R. W., and Smith, G. V.: A Ten Year Analysis of Thromboembolism and Dicumarol Prophylaxis. Surg., Gynec. & Obst. **98:** 437 (Apr.), 1954.

In order to study the prophylactic use of Dicumarol, 6,705 Dicumarol-treated women undergoing surgery were compared with a control group of 18,852 patients. In the treated series, hemorrhagic complications were infrequent and without mortality. There were eight deaths (0.031 per cent) from pulmonary embolism and 20 cases (0.078 per cent) of nonfatal pulmonary embolism. In the control series the incidence of fatal emboli was 0.085 per cent and of nonfatal emboli, 0.020 per cent.

The authors concluded that although the use of Dicumarol could not be demonstrated unequivocally to have been of value, the various results strongly indicated that it was a factor in achieving the improved figures.

ABRAMSON

Lawrence, W. E., Kahn, S. S., and Riser, A. B.: A Comparative Study of the Clinical Effects of Oral and Parenteral Mercurial Diuretics in 70 Patients with Congestive Heart Failure. South. M. J. **47:** 105 (Feb.), 1954.

Seventy selected ambulatory patients with chronic congestive failure were administered extended successive courses of Meralluride parenterally and Neohydrin orally as the only diuretic in the regimen of treatment. Ninety-seven per cent of these appeared to do as well or better on the oral preparation than on the parenteral. Thirty-five per cent of 60 patients given placebos after successful maintenance on Neohydrin continued to maintain compensation without the apparent need for a diuretic. The remainder reverted to congestive failure over periods ranging from one week to five months.

Changes in body weight were helpful as criteria in estimating the degree of compensation in certain individuals but could not be depended upon as a general rule. Mean body weight changes during the course on Neohydrin were not statistically significant. Toxic manifestations and side effects were encountered in patients receiving Neohydrin. These were of a minor nature except in one patient who could not tolerate the preparation because of persistent diarrhea and in two patients who required full mouth extractions because of severe gingivitis.

BERNSTEIN

Gourzio, J. T., Sonnenschein, R. R., and Barden, R.: Alterations in Cardiovascular Responses of the Dog Following Rauwiloid, An Alkaloidal Extract of Rauwolfia serpentina. Proc. Soc. Exper. Biol. & Med. **85:** 436 (Mar.), 1954.

An attempt was made to observe hypotensive effects of Rauwiloid (a mixture of alkaloids extracted from the root of Rauwolfia serpentina known to possess the total activity of the root) on cardiovascular response of normotensive dogs. Fifteen dogs were dosed for 5 days with 0.5 mg. per kilogram of body weight per day. On the sixteenth day under anesthesia, acute experiments were performed. Fifteen other dogs served as controls. Though the mean arterial blood pressure and heart rate diminished, the change was not statistically significant. The pressor response to a low dose of epinephrine

intravenously (1.0 microgram), was higher in medicated animals than in normals, but with higher doses of epinephrine (3.0 microgram), the response was the same. The data show no statistical difference in depressor response from Isuprel in the two groups. Blood pressure in all treated animals fell in response to hypoxia in contrast to that in controls which rose in the usually expected fashion. The hypotensive response to acetylcholine, histamine, and efferent vagal stimulation was unaltered.

HARVEY

Degenhardt, D. P., and Hodgkinson, R.: Ethaverine in the Treatment of Angina Pectoris. Brit. Heart J. **16:** 142 (Apr.), 1954.

An attempt was made to evaluate the ethyl analogue of papaverine in the treatment of angina pectoris. One hundred milligrams four times a day was used. Twenty-two patients were studied by the double blindfold method. Ethaverine had no greater effect than inert lactose.

SOLOFF

Martini, L., and Rovati, V.: Actions of an Adrenolytic Drug (Regitine) on Carotid Sinus Walls. Arch. Internat. Pharmacodyn. **67:** 420 (Apr. 1) 1954.

Experiments on anesthetized dogs, with vagi-aortic nerves cut, showed that:

Local application of Regitine on carotid sinus walls induces a marked and prolonged reflex rise of systemic arterial pressure. The hypertensive reflexes of carotid sinus origin (clamping of both common carotid arteries) are unaffected.

After reflex lowering of the systemic arterial pressure, and suppression of the vasopressor carotid sinus reflexes, induced by local application of adrenaline on carotid sinus walls, the local application of Regitine on the same areas produces a progressive and marked increase of general pressure. It rises to values above the initial ones. The vasopressor reflexes of carotid sinus origin are restored.

After reflex lowering of the systemic arterial pressure, and suppression of the vasopressor carotid sinus reflexes, induced by local application of noradrenaline on carotid sinus walls, the local application of Regitine on the same areas produces a progressive increase of general pressure, reaching only the initial values. The vasopressor reflexes of carotid sinus origin are restored.

These experiments are consistent with the hypothesis that the action of Regitine (which has no direct vasodilating action), when applied on the carotid sinus walls, is due to its capacity for reversing (from constricting to dilating) the action—on intrinsic tone of the walls of the arteries, where the pressoceptors are located—of the adrenaline which is contained in the walls of the arteries themselves.

These experiments emphasize the importance of the adrenaline contained in the walls of the arteries in the maintainence and regulation of the intrinsic tone and resistance to stretch of the arteries where the pressoceptors are located.

AUTHORS

Tripod, J., Bein, H. J., and Meier, R.: Characterization of Central Effects of Serpasil (Reserpin, A New Alkaloid of Rauwolfia Serpentina B) and of Their Antagonistic Reactions. Arch. Internat. Pharmacodyn. **67:** 406 (Jan. 1), 1954.

Serpasil, a new alkaloid of Rauwolfia serpentina B., produces a peculiar depression of the central nervous system characterized by a prolonged and marked sedation and miosis, and by some antipyresis. Serpasil also shows a marked antagonism to psychomotor stimulations centrally elicited by caffeine, morphine, scopolamine and cocaine, but not by pervitin. On the other hand, Serpasil does not counteract central convulsants like strychnine, nicotine, picrotoxin and Metrazol, but antagonizes audiogenic seizures. In most of these antagonistic tests, Serpasil acts differently from phenobarbital and sodium bromide. Its sedative effect is also influenced by parasympatholytic and sympatholytic agents in a way different from that of the two other central depressants, and it also counteracts differently the miosis produced by various agents. The significance of these comparative findings is analyzed and discussed.

AUTHORS

Haymond, T., and Bellet, S.: Effect of Banthine on the Cardiac Mechanism in States Associated with Increased Vagal Tone. Am. J. Med. **16:** 516 (Apr.), 1954.

Banthine (5 to 10 mg.) administered intravenously to 11 patients and orally (100 to 400 mg. daily) to eight patients proved to be an efficacious agent in combating excessive vagal tone involving the cardiovascular system. Following the intravenous administration of banthine, tachycardia and shortening of the P-R interval occurred within 45 to 90 seconds. These effects persisted for four to six hours. Oral Banthine produced a moderate tachycardia within 30 minutes to one and one-half hours which persisted three to six hours. The carotid sinus reflex was abolished in all six cases when the oral route was used. Relatively large, therapeutically effective doses of Banthine can be administered with fewer side effects than are observed with comparable doses of atropine. The tested subjects included patients with A-V heart block (six cases), hypersensitive carotid sinus syndrome (six cases), Wolff-Parkinson-White syndrome and coronary sinus rhythm (one case each).

HARRIS

Rezende, N., and Essex, H. E.: Regional Administration of Various Substances Intra-Arterially and into the Left Ventricle of Dogs. Proc. Staff Meet. Mayo Clinic **29:** 163 (Mar. 24), 195

Antibiotics and certain drugs were introduced into the canine arterial system to determine whether they were tolerated as well when administered by this route as when they were administered by other routes commonly used. The drugs were injected into either common carotid or either femoral artery of dogs by means of a needle or by a catheter introduced into the vessel. The use of catheters with balloons attached made it possible to limit the injection to a specific artery, such as the renal. This method has a distinct advantage in that it makes it possible to investigate the effects of drugs introduced in high concentration directly into an organ. Thus the passage of the material through the circulation of either the liver or the lungs or both, with a resultant decrease in its concentration, can be avoided. Injections were made into the brain, fundus of the eye, lungs, heart, stomach, pancreas, spleen, kidneys and male and female genitalia of the animals.

Injection of the drugs into the left side of the heart and into other organs was rapid in some cases and slow (1 cc. per minute) in others. Immediate deleterious effects on the animals were not observed. Several dogs were kept for as long as three weeks after the injection of certain antibiotics and drugs into the left ventricle. They were unaffected by the treatment insofar as could be determined by the arterial blood pressure, the electrocardiogram and the gross appearance of the various organs. The introduction of antibiotics and other drugs into the arteries was well tolerated as attested by the fact that 120 experiments on dogs were done without a single untoward result.

SIMON

Marquez, M. G., and Rato, J. A.: Some Effects of Ergot Alkaloids Upon the Cardiovascular System. Cardiologia **24:** 196 (Fasc. 4), 1954.

The effect of a single intravenous dose of 0.3 mg. Hydergine was studied in five normotensives and 20 hypertensive persons. The systolic pressure invariably dropped, whereas the diastolic pressure was only slightly and inconstantly affected. The reduction of systolic pressure was abrupt and persisted for about one hour; it was most marked when the initial values were high. The heart slowed by about 8 to 12 beats per minute and at times this was preceded by a slight, transient acceleration. Insignificant electrocardiographic alterations occurring during the experiments consisting mainly of a shift of the QRS axis. In two hypertensive patients who developed acute pulmonary edema in spite of complete digitalization, rapid and complete recovery took place after intravenous injection of Hydergine. In the opinion of the authors, this justifies a more detailed study of the effect of the drug under such circumstances.

PICK

Smith, D. J.: Immediate Sensitization of Isolated Swine Arteries and Their Vasa Vasorum to Epinephrine, Acetylcholine and Histamine by Thyroxin. Am. J. Physiol. **177:** 7 (Apr.), 1954.

The sensitivity of excised swine arteries to *l*-epinephrine is increased by thyroxin. Both the amount and duration of the response is increased. Reaction to acetylcholine is slightly prolonged. Histamine vasoconstriction is shortest at 1 to 10 million concentration, above and below which the response duration is increased. The flow through vasa vasorum was decreased in vessels from thyroidectomized swine. Thyroxin alone does not constrict either the arterial walls or vasa vosorum but prolongs extensively the duration of constriction caused by *l*-epinephrine.

OPPENHEIMER

Weingarten, W., Galluzzi, N. J., and Doerner, A. A.: Cardiac Arrest after Intravenous Administration of Procaine Amide (Pronestyl). J. A. M. A. **154:** 985 (Mar. 20), 1954.

A case of cardiac standstill is reported following intravenous administration of procaine amide. In this case there was marked widening of the QRS complexes (which is known to be a side reaction of procaine amide administration) after each dose of procaine amide given prior to the last dose which caused the complete cardiac arrest. Continuous electrocardiographic tracings were taken during the administration of the drug and revealed immediate changes after each dose, so the relationship between the administration of procaine amide and cardiac arrest seems well established.

KITCHELL

Heymans, C., Delaunois, A. L., and Martini, L.: Hexamethonium and Conduction and Excitability in the Vagal Center. Arch. Internat. pharmacodyn. **67:** 313 (Apr. 1), 1954.

From experiments on dogs, using the method of the isolated perfused head connected with its trunk by means of the vagi nerves only, it is shown that intra-arterial injections of high doses of hexamethonium into the isolated and perfused head do not interfere with the processes of reflex transmission and direct excitation in the cardio-inhibitory vagal center. These observations add other evidence that central and autonomic ganglionic transmission and excitability react in a different way to ganglionic blocking agents.

AUTHORS

Prevedel, A. E., Montgomery, V., and Swan, H.: Effect of Coronary Perfusion of Prostigmin on Ventricular Fibrillation in the Hypothermic Dog. Proc. Soc. Exp. Biol. & Med. **85:** 598 (Apr.), 1954.

Anesthetized mongrel dogs were made hypo-

thermic (23 C. rectally) by immersion in ice water. A right thoracotomy was performed and the heart exposed, both cavae and aorta occluded. A right ventriculotomy was performed. In 23 control dogs this produced ventricular fibrillation. Massage and electroshock could not defibrillate. In 8 of 15 dogs given Prostigmin intravenously (0.05 ml. of 1 to 4,000 solution per kilogram of body weight before inflow occlusion was effected) no fibrillation occurred. In five of the animals with fibrillation, resuscitation was successful. In 16 animals given Prostigmin by injection into the base of the aorta effecting coronary perfusion, no fibrillation occurred. The same type of results were obtained when the stimulus to produce fibrillation was catheterization of the coronary sinus in the hypothermic dog.

HARVEY

O'Brien, G. S., Rockey, J., Murphy, Q. R. Jr., and Meek, W. J.: The Effect of Digitoxin and Digoxin on Cardiac Rhythm and Arterial Plasma Potassium before and after Epinephrine Injection in Unanesthetized Dogs. II. Texas Rep. Biol. & Med. **2:** 602 (Winter), 1953.

From these studies it is evident that in most unanesthetized dogs digitoxin and digoxin increased the sensitivity of the heart to an intravenous injection of epinephrine. One hour after digitoxin or Digoxin the arterial plasma potassium was at a higher level than normal, and although the actual rise which followed a subsequent injection of epinephrine was slightly less than in the normal animal, the level reached was much higher in most animals. It may be considered that the potassium in these animals had now reached a critical level which possibly had an effect on the production of arrhythmias. It was noted invariably that the cardiac arrhythmias produced by epinephrine after digitoxin or Digoxin were definitely related in time to the elevation of plasma potassium produced by the epinephrine.

BERNSTEIN

Rosenman, R. H., Byers, S. O., and Friedman, M.: The Effect of Soybean Sterols on the Absorption of Cholesterol by the Rat. Circulation Research **2:** 160 (Mar.), 1954.

The inhibitory effect of soybean sterols on the intestinal absorption and plasma levels of cholesterol was studied in the rat. Mixed soybean sterols (80 per cent sitosterols) were fed to rats simultaneously with cholesterol. In acute experiments, the total cholesterol content of 24 hour lymph collections was essentially the same in the control, cholesterol-fed rats as in the rats simultaneously fed both cholesterol and soybean sterols, illustrating that the soybean sterols did not interfere with the intestinal absorption of cholesterol. In chronic experiments, the addition of 2 or 10 per cent soybean sterols to a diet which induces chronic hypercholesterolemia in rats failed to inhibit the development or magnitude of the hypercholesterolemia.

MAXWELL

Bicherman, H. A., and Barach, A. L.: The Effect of Cigarette Smoking on Ventilatory Function in Patients with Bronchial Asthma and Obstructive Pulmonary Emphysema. J. Lab. & Clin. Med. **43:** 455 (Mar.), 1954.

A study of the acute effects of tobacco smoking on the ventilatory function was made on 91 patients with chronic nontuberculous pulmonary disease, and 27 normal, healthy, young adults. All the patients and control subjects were mild habitual smokers. All of the patients had pulmonary disease with which there was some degree of associated bronchospasm. Ventilatory function was measured before and after smoking three cigarettes. In the majority of patients and all control subjects no change in ventilatory function or evidence of bronchospasm was found by measuring vital capacity or maximum breathing capacity. In 10 patients there was slight reduction of these two measurements, but there was no subjective change. In nine patients, smoke-induced cough increased vital capacity and maximum breathing capacity for considerable sputum was expectorated as a result of the irritation and coughing.

HARVEY

PHYSICAL SIGNS

McKusick, V. A., Talbot, S. A., and Webb, G. N.: Spectral Phonocardiography: Problems and Prospects in the Application of the Bell Sound Spectrograph to Phonocardiography. Bull. Johns Hopkins Hosp. **94:** 187 (Apr.), 1954.

Technical modifications of the Bell sound spectrograph for its application to phonocardiography are described. These include the design of a filter system which provides optimum simultaneous resolution in both time and frequency instrumentation for parallel recording of other physiologic events, provision of a logarithmic frequency scale, conversion from direct-written to photographic records for improved definition in the intensity dimension. This method incorporates the three dimensions of heart sounds in a single detailed display. Time is the abscissa and frequency spectrum the ordinate; intensity is indicated by degree of brightness or blackness depending on the type of record employed.

Spectral phonocardiograms resemble closely the mental image of heart sounds and murmurs. Their interpretation is easy and teaching value considerable. Quality of murmurs is displayed as illustrated by an instance of "cooing" aortic diastolic murmur which shows conspicuous harmonics with a characteristic curvature.

MCKUSICK

Reinhold, J. D. I., and Nadas, A. S.: The Role of Auscultation in the Diagnosis of Congenital Heart Disease, Phonocardiograph Study of Children. Am. Heart J. **47:** 405 (Mar.), 1954.

Sixty-four patients with congenital heart disease were studied by means of phonocardiography. This included aortic stenosis, isolated pulmonary valvular stenosis, ventricular septal defect and single ventricle, ventricular septal defect, tetralogy of Fallot, and atypical patent ductus arteriosus. The murmurs and the valvular elements of the heart sounds are described in these defects. The value of auscultation and phonocardiography is stressed in the differential diagnosis of these conditions.

RINZLER

Sjoerdsma, A., and Gaynor, W. B.: Contraction of Left Leaf of Diaphragm Coincident with Cardiac Systole. J. A. M. A. **154:** 987 (Mar. 20), 1954.

Report is made of clonic contractions of the left leaf of the diaphragm synchronous with the heart beat in a 40 year old man with alkalosis and latent tetany. Three other cases are cited from the literature. There was hypocalcemia in one case and alkalosis in the other two. It is postulated that, in the presence of the increased neuromuscular excitability of tetany, electrical stimulation of the left phrenic nerve by the heart's action currents may produce contraction of the left leaf of the diaphragm.

KITCHELL

PHYSIOLOGY

Davis, J. O., Howell, D. S., Laqueur, G. L., and Peirce, E. C., II: Renal Hemodynamic Function, Electrolyte Metabolism and Water Exchange in Adrenalectomized-Hypophysectomized Dogs. Am. J. Physiol. **176:** 411 (Mar.), 1954.

There is a decrease in kidney function when either hypophysectomy or thyroidectomy is performed in adrenalectomized dogs. As a result of this observation it may be concluded that the change in kidney circulation in the hypophysectomized animal is not due to loss of corticotropin alone. The glomerular filtration rate and renal plasma flow was increased by thyrotropin or growth hormone in dogs deprived of adrenal and pituitary. Loss of thyrotropin and growth hormone may explain decreased kidney function after removal of the pituitary in previously adrenalectomized dogs. It was possible to support adrenalectomized-hypophysectomized dogs without the use of hormones by use of a high sodium diet. Desoxycorticosterone acetate or cortisone would also maintain them. Removal of the pituitary in adrenalectomized dogs produced a diabetes insipidus of short duration. Elevated gomerular filtration rate was well correlated with increased water exchange during use of growth hormone and thyrotropin.

OPPENHEIMER

Warner, H. R.: Quantitation of Stroke Volume Changes in Man from The Central Pressure Pulse. Minnesota Med. **37:** 111 (Feb.), 1954.

A method of measuring stroke volume in man from a recording of a central and a peripheral pressure pulse has been presented. This requires the obtaining of a factor relating change in arterial pressure to change in volume, by carrying out a determination of stroke volume during a steady state period by an independent method. Inasmuch as the usefulness of a pressure pulse method lies primarily in its ability to follow rapid changes in stroke volume, this would not appear to be a serious disadvantage. Basically, this approach differs from that of others in the assumption of a linear volume-pressure relationship, the slope of which is measured in each individual, while others accept this individual variation by utilizing an average curve.

BERNSTEIN

Chapman, W. P., Wilkins, E. W. Jr., and Von Hueber, E.: Electrical Stimulation of the Central End of the Vagus Nerve in the Unanesthetized Dog—Method and Effects on Gastrointestinal, Respiratory, and Circulatory Systems. Surg., Gynec. & Obst. **98:** 353 (Mar.), 1954.

The authors studied vagal reflexes under conditions free of the modifying influences of drugs or anesthesia. A method of electric stimulation has been worked out in which bipolar electrodes can be left in place on the central cut end of the vagus nerve. Such a study has been made in eight dogs in whom electrical stimulation has been performed from 2 to 10 days following electrode implantation. In all the experiments, observations were made of the effect of electrical stimulation of the central end of the vagus nerve on retching and vomiting. In three dogs electrical stimulation of the vagus nerve was also studied for its effect on the continuous registration of heart rate, blood pressure and respirations.

Electrical stimulation produced changes in breathing, retching, and under certain conditions, vomiting. Retching or vomiting was associated with slowing of the heart rate and an increase in pulse pressure. This response was obtained from electrical stimulation of either vagus nerve and persisted when both vagus nerves had been cut.

The intravenous administration of apomorphine simulated the effects of electrical stimulation of the central end of the vagus with respect to retching, slowing of heart rate, and increase in pulse pressure.

The intravenous administration of large doses of atropine abolished the slowing of heart rate and increase in pulse pressure in response to electrical stimulation or apomorphine administration but not the retching or respiratory effects.

The intravenous administration of Nembutal in sufficient doses to cause anesthesia abolished the retching and circulatory effects of electrical stimula-

tion of the vagus nerve. Changes in breathing were elicited but they were of a different type from that noted when only electrical stimulation was employed.

DENNISON

RHEUMATIC FEVER

Saslaw, M. S., Hernandez, F. A., and Werblow, S. C.: Conditions Clinically Confused with the Rheumatic State. J. Pediat. **44:** 414 (Apr.), 1954.

Case records of 2,045 outpatients suspected of having rheumatic or congenital heart disease were reviewed. It was found that 46.8 per cent had no heart disease, 23.5 per cent were in the "rheumatic state," and 23.6 per cent had congenital lesions.

Nonrheumatic conditions, in which prolonged fever, joint pain, and heart murmur were part of the picture, were mistakenly diagnosed as rheumatic fever or rheumatic heart disease in 117 cases (5.7 per cent). The signs and symptoms which confused these conditions with the rheumatic state and those which determined the final diagnoses were tabulated and discussed, with special emphasis on methods of preventing such mistaken diagnoses.

MAXWELL

Lehman, J. S., and Curry, J. L.: A Correlation of Roentgen and Surgical Findings in Two Hundred Cases of Rheumatic Mitral Valvular Disease. Evaluation of Cardiac Chamber Size, Valvular Calcification and Pulmonary Vessels. Am. J. Roentgenol. **71:** 599 (Apr.), 1954.

Correlated roentgen and surgical findings are presented in 192 cases explored for the relief of mitral stenosis and in eight cases where surgical efforts were directed to the relief of mitral insufficiency as the dominant lesion.

Roentgenologic estimate of right ventricular enlargement seems reasonably accurate, as is the degree of left atrial enlargement. Carinal widening, in general, parallels the degree of esophageal displacement. The authors experienced greatest difficulty in estimating left ventricular size, citing difficulties in estimating the point of differential pulsations, inability to identify the interventricular notch. The position of the cardiac apex seems to be the most reliable single guide in predicting left ventricular size.

Accuracy of roentgenologic detection of mitral valve calcification has been high. The size of the major pulmonary vessels visible to the surgeon was usually greater than estimated roentgenologically.

Determination of the presence and degree of mitral insufficiency in clinically uncertain cases presents a roentgenologic problem. Estimation of left ventricular size is important but often difficult in larger hearts. Systolic expansion of the left atrium is a possible but unreliable guide. Multiple slit kymography has proved discouraging as a possible contribution to the solution of the problem.

SCHWEDEL

McCue, C. M.: A Follow-up Study of Suspected Rheumatic Fever Patients. J. Pediat. **44:** 390 (Mar.), 1954.

Among 2,678 new patients seen between 1941 and 1952 in the Rheumatic Fever Clinic of the Medical College of Virginia, the diagnosis was deferred on the initial visit of 236 patients. The deferrals were made by the consultant because there was lack of evidence of clear-cut signs and symptoms of rheumatism in each individual. Vague muscle aches, joint pains, slight fever, or a questionable murmur had led the referring physician to suspect rheumatic fever. Follow-up studies were done from three months to 10 years after the initial visit with the average slightly over two years; 209 of these patients were re-examined. One hundred sixty-seven patients (79.9 per cent) were shown reasonably well not to have rheumatic infection; 29 patients (13.8 per cent) clearly had rheumatic infection. In 13 patients (6.2 per cent), the diagnosis was still deferred.

HARVEY

Wallach, J. B., Lukash, L., and Angrist, A. A.: The Mechanism of Formation of Left Auricular Mural Thrombi. Am. J. Med. **16:** 543 (Apr.), 1954.

Significant factors associated with formation of thrombi in the left atrium were studied in 509 consecutive autopsied cases of rheumatic heart disease. These factors include valvular distortion, nonbacterial thrombotic endocarditis, age of the patient and duration of the disease, auricular fibrillation, alterations in the clotting mechanism, subacute bacterial endocarditis, auricular infarction and rheumatic activity. Embolization is responsible for death in more than 20 per cent of the patients who die of rheumatic heart disease, and in an additional number emboli may cause serious and permanent disability.

The mechanical effects of impingement of a regurgitant jet of blood upon the auricular wall with each ventricular contraction in the presence of mitral insufficiency and stenosis leads to collagenous thickening of the endocardium at that site. Devitalization of such auricular endocardium by any of several mechanisms, including physical trauma and other injuries most of which remain unknown, favors the formation of nonbacterial thrombotic endocarditis at this site. It is presumed that this nonbacterial nidus offers a starting point for the deposition of the mural thrombus. In rheumatic hearts mural thrombi occur more frequently in the left than in the right auricle because (1) stenosis and insufficiency of the mitral valve are more common

and more severe than of the tricuspid valve, and (2) the force imparted to the regurgitant stream of blood is greater because the systolic pressure in the left ventricle considerably exceeds that in the right ventricle. The greater incidence of auricular mural thrombi noted with increased age and with the presence of auricular fibrillation is only a reflection of the longer duration of the disease during which the altered hemodynamics may produce the local changes described.

HARRIS

Poppi, A., Labo, G., Lenzi, G., and Rosa, L.: Epidemiology of Rheumatic Fever in a Rural District in Italy. Ann. Rheumat. Dis. **12:** 310 (Dec.), 1953.

A sample of the population of the rice growing area of the lower Po valley was examined. Of 930 women, aged 14 to 70 years, 607 were rice field workers and 323 were manual workers otherwise employed. Rheumatic fever, rheumatic heart disease, and atypical rheumatic manifestations occurred in 24, 11 and 17 per cent, respectively, among the rice field workers as compared with 7, 3, and 11 per cent among the other workers. There is, thus, a close connection with the type of employment as well as the poor conditions of life.

BERNSTEIN

Yu, P. N. G., Simpson, J. H., Lovejoy, F. W. Jr., Joos, H. A., and Nye, R. E. Jr.: Studies of Pulmonary Hypertension. IV. Pulmonary Circulatory Dynamics in Patients with Mitral Stenosis at Rest. Am. Heart J. **47:** 330 (Mar.), 1954.

Physiologic data at rest are presented on 43 patients with predominant mitral stenosis. In general, the more severely disabled patients manifested higher pulmonary artery and "capillary" pressures, wider pulmonary artery–pulmonary "capillary" mean pressure gradient, and higher pulmonary resistance. They had lower cardiac index, stroke index, and arterial blood oxygen saturation. Twenty-nine of the 31 patients whose pulmonary artery mean pressure exceeded 30 mm. Hg had a calculated mitral valve area of 1.0 sq. cm. or less. Pulmonary "capillary" pressure was found to correlate with pulmonary artery diastolic and mean pressures, but not with pulmonary arteriolar resistance. When the pulmonary artery diastolic pressure is less than 30 mm. Hg, it may be substituted for pulmonary "capillary" pressure in the formula of Gorlin and Gorlin in calculating mitral valve area.

RINZLER

Rapport, S. I., Meister, L., Steele, F. M., and Caniglia, S. R.: Pulmonary Lesions of Disseminated Lupus Erythematosus. Ann. Rheumat. Dis. **12:** 268 (Dec.), 1953.

The published descriptions of pulmonary parenchymal lesions in disseminated lupus erythematosus are reviewed and two cases are reported which illustrate the clinical manifestations of such lung lesions. An awareness of their frequency and atypical behavior is necessary for two reasons: (1) to recognize cases in which pulmonary infiltrates are the major symptom of disease; and (2) to differentiate, in established cases, primary parenchymal disease from a secondary infective pneumonia.

In the first patient here reported, a bilateral, shifting pneumonitis with pleuritis so overshadowed evidence of other organic involvement that an extensive search was made for primary pulmonary disease. In the second patient, the combination of bilateral pulmonary infiltrates, peripheral lymphadenopathy, and polyarthritis closely mimicked sarcoidosis with polyarthritis, and rheumatoid lung disease. A correct diagnosis was established only after the demonstration of typical L.E. cells. The response of the pulmonary lesions to corticotropin therapy varied; in one patient there was complete clearing, and in the other the pulmonary lesions remained unchanged despite corticotropin therapy sufficient to induce a pronounced Cushing effect.

BERNSTEIN

ROENTGENOLOGY

Johnsson, G., Broden, B., and Karnell, J.: Angiocardiographic Demonstration of Pulmonary Stenosis. Acta radiol. **40:** 547 (Dec.), 1953.

The authors recommend selective angiocardiography, passing a catheter directly into the right ventricle before injecting the opacifying solution, and taking films in posteroanterior and lateral views preferably simultaneously and rapidly (six exposures per second) to secure the best visualization of pulmonic, valvular, or infundibular stenosis. The method does not entail any greater risk than other forms of angiocardiography or cardiac catheterization.

SCHWEDEL

Garlan, L. H., and Sisson, M. A.: Roentgen Findings in the "Collagen" Diseases. Am. J. Roentgenol. **71:** 581 (Apr.), 1954.

The authors present a review of the roentgenologic aspects in 28 cases of polyarteritis, 32 cases of generalized lupus erythematosus, one case of dematomyositis and 25 cases of scleroderma. They believe that nonspecific pleural and pulmonary changes are frequently present. Pericardial effusion and cardiac enlargement occur less frequently, and may be reversible.

Abdominal distension, with paralytic obstruction, and renal enlargement, at times, may be demonstrable in polyarteritis and lupus. In scleroderma about one-half of the cases show intestinal or esophageal changes. Articular and osseous changes,

including calcinosis, are found most often in scleroderma.

SCHWEDEL

SURGERY

Frymark, W. B., and Sullivan, J. M.: Lumbar Sympathectomy for Arteriosclerotic Peripheral Vascular Disease. Ann. Surg. **138:** 759 (Nov.), 1953.

A study was made of the results obtained with lumbar sympathectomy in a series of 79 patients with arteriosclerosis obliterans. It was found that intermittent claudication improved in only 40 per cent of cases. Of the 22 extremities with gangrene preoperatively, in four the gangrenous portion had been amputated before sympathectomy and no further extension of the gangrene was noted. In five cases the gangrenous portion was amputated after sympathectomy, and again there was no spread. In 17 instances gangrene developed subsequent to sympathectomy and in every case the limb was amputated. Of the entire series, 26 extremities (23 per cent) were lost by amputation, despite sympathectomy.

It was concluded that over three-fifths of the patients obtained some benefit from lumbar sympathectomy.

ABRAMSON

Craig, W. M.: Sympathectomy for Occlusive Arterial Disease. Proc. Staff Meet., Mayo Clin. **29:** 143 (Mar.), 1954.

The condition of the patient who has obliterating endarteritis associated with arteriosclerosis was thought at first to be such that it would not respond to sympathectomy. Originally, little vasomotor spasm was thought to be associated with this disease and therefore the condition was thought not to be amenable to surgery. This attitude has changed and surgical measures now are applied to the treatment of peripheral vascular disease of the occlusive type if it is not associated with gangrene and if the circulation can be improved with vasodilators. The age limit for surgical treatment in obliterating endarteritis associated with arteriosclerosis was first set at 60 years. Now, however, the condition of the extremity involved is the criterion which guides the surgeon in selection of patients. Contraindications to surgical treatment consist of associated coronary disease, debilitation and extreme arteriosclerosis with no demonstrable vasomotor change on the administration of vasodilating drugs or after the injection of the sympathetic ganglia with procaine hydrochloride.

Sympathetic block as a preliminary procedure to test the value of sympathectomy is not an entirely dependable test except, perhaps, among patients who have severe, intractable pain or ischemic neuritis. Sympathectomy is considered the method of choice in the treatment of arteriosclerotic peripheral vascular disease unless there exist definite contraindications

SIMON

Giberson, R. G., Waugh, J. M., Hines, E. A., and Faulconer, A., Jr.: Chronic Occlusive Disease of the Terminal Aorta and its Surgical Treatment. Proc. Staff Meet., Mayo Clin. **29:** 137 (Mar.), 1954.

Chronic progressive occlusion of the terminal aorta arising from arteriosclerotic changes and superimposed thrombosis causes a syndrome characterized by the symptoms and signs of bilateral arterial insufficiency in the lower extremities. Bilateral lumbar sympathectomy, with thromboendarterectomy or excision of the occluded area and replacement of the removed portion by graft, has been reported to give relief. A case in which a patient was treated by thromboendarterectomy and bilateral lumbar sympathectomy is presented. The results of surgical treatment in this case are encouraging, but the role of surgery in the treatment of occlusive arterial disease of the terminal aorta has not been definitely assessed at this time.

SIMON

Zimmerman, H. A., and Kay, E. B.: Use of Direct Pressure Measurement at the Operating Table to Evaluate the Acute Results of Corrective Cardiac Surgery. J. Thoracic Surg. **27:** 425 (Apr.), 1954.

A simple method is described for taking direct pressure at the time of cardiac surgery. It consists of a Statham pressure transmitter, filled with aqueous Zephiran chloride, 1 per cent, and the nub of the gage, filled with heparin, 10 mg. per cubic centimeter. The sterile nub is connected to a 22 or 23 gage needle which is placed in the desired area to record pressures. The recording system consists of strain gage amplifiers of the Photron or Sanborn type, which feed the signal into a single or double channel direct-writing recorder.

ABRAMSON

AMERICAN HEART ASSOCIATION, INC.

44 East 23rd Street, New York 10, N. Y.

Telephone Gramercy 7–9170

The article which follows is a revision of the American Heart Association statement on the prevention of rheumatic fever issued January, 1953. This revision has become necessary as knowledge concerning effective technics of control of streptococcal infections is increasing.

PREVENTION OF RHEUMATIC FEVER AND BACTERIAL ENDOCARDITIS THROUGH CONTROL OF STREPTOCOCCAL INFECTIONS*

Rheumatic fever is a recurrent disease which in most instances can be prevented. Since both the initial and recurrent attacks of the disease are precipitated by infections with beta hemolytic streptococci, prevention of rheumatic fever and rheumatic heart disease depends upon the control of streptococcal infections. This may be accomplished by (1) early and adequate treatment of streptococcal infections in *all* individuals and (2) prevention of streptoccocal infections in *rheumatic* subjects.

I. Treatment of Streptococcal Infections in the General Population

In the general population about 3 per cent of untreated streptococcal infections are followed by rheumatic fever. Adequate and early penicillin treatment, however, will eliminate streptococci from the throat and prevent most attacks of rheumatic fever.

A. Diagnosis of Streptococcal Infection

In many instances streptococcal infections can be recognized by their clinical manifestations. In some patients, however, it is difficult or impossible to determine the streptococcal nature of a respiratory infection without obtaining throat cultures. The following section on diagnosis has been included in order to reduce diagnostic errors and to assist physicians in avoiding unnecessary therapy.

The accurate recognition of individual streptococcal infections, their adequate treatment and the control of epidemics in the community presently offer the best means of preventing initial and recurrent rheumatic fever.

1. Common Symptoms

a. Sore throat—sudden onset, pain on swallowing.

b. Headache—common.

c. Fever—variable, but generally from 101 to 104 F.

d. Abdominal pain—common, especially in children; less common in adults.

e. Nausea and vomiting—common, especially in children.

f. In the absence of the common symptoms and signs, occurrence of one of the following symptoms is usually not associated with a streptococcal infection: (1) simple coryza, (2) hoarseness, (3) cough.

2. Common Signs

a. Red throat.

b. Exudate—usually present.

c. Glands—swollen, *tender* lymph nodes at angle of jaw.

d. Rash—scarlatiniform.

e. Acute otitis media and acute sinusitis are frequently due to the streptococcus.

3. Laboratory Findings

a. White blood count—generally over 12,000.

b. Throat culture—positive culture for hemolytic streptococci is almost always diagnostic.

B. Treatment of Streptococcal Infections

When streptococcal infection is suspected, treatment should be started immediately. Penicillin is the drug of choice. Effective blood levels should be maintained for a *period of ten days* to prevent rheumatic fever by eradicating the streptococci from the throat.

Penicillin may be administered by either intramuscular or oral route. Intramuscular administration is recommended as the method of choice since it insures adequate treatment. Oral therapy by contrast is dependent upon the cooperation of the patient. On the other hand, some physicians and patients prefer repeated oral medication and object to injections.

C. Recommended Treatment Schedules

1. Intramuscular Penicillin

a. Benzathine Penicillin G: (1) *Children*—one intramuscular injection of 600,000 units. (2) *Adults*—one intramuscular injection of 600,000 to 900,000 units; *or*

b. Procaine penicillin with aluminum monostearate in oil: (1) *Children*—one intramuscular injection of 300,000 units every third day for three

*This statement was prepared by the Committee on Prevention of Rheumatic Fever and Bacterial Endocarditis appointed by the Council on Rheumatic Fever and Congenital Heart Disease of the Association. The committee is cognizant of the fact that no recommendations can be final at this time. Revision will be made as new knowledge may indicate.

doses. (2) *Adults*—one intramuscular injection of 600,000 units every third day for three doses.

2. Oral Penicillin

Children and adults—250,000 units three times a day for a full ten days.

To prevent rheumatic fever by eradicating streptococci, therapy must be continued *for the entire ten days* even though the temperature returns to normal and the patient is asymptomatic.

3. Other Medication

It has not been established that the broad spectrum antibiotics are as effective as penicillin in preventing rheumatic fever. They should be used only if the patient is sensitive to penicillin. As with penicillin, the regimen of full therapeutic dosage for a full ten days should be followed.

The following therapy is *not effective* in preventing rheumatic fever when used as treatment for streptococcal infections: (a) sulfonamide drugs, (b) penicillin troches or lozenges.

II. Prevention of Streptococcal Infections in Rheumatic Individuals

Many streptococcal infections occur without producing clinical manifestations. For this reason, prevention of recurrent rheumatic fever must depend on continuous prophylaxis rather than solely on treatment of acute attacks of streptococcal disease.

A. General Rules for Prophylaxis

1. Who should be treated?

All individuals who have a well established history of a previous attack of rheumatic fever or chorea or who show *definite* evidence of rheumatic heart disease should be placed on continuous prophylaxis.

2. When should prophylactic treatment be initiated?

a. Active rheumatic fever

As soon as the diagnosis of rheumatic fever is made or any time thereafter when the patient is first seen. The streptococcus should be eradicated with penicillin (see under I-C, Treatment) following which the prophylactic regimen is instituted.

b. Inactive rheumatic fever

In inactive rheumatic fever, prophylaxis should be instituted when the patient is first seen.

3. How long should prophylaxis be continued?

Throughout life, or until new knowledge makes this recommendation invalid.

4. Should prophylaxis be continued during the summer?

Yes, continuously. Streptococcal infections can occur at any season although they are more prevalent in the winter.

5. What are the exceptions to continuous prophylaxis?

a. Uncertainty as to the validity of a history of a previous attack of rheumatic fever or chorea.

b. Heart disease of questionable etiology.

c. In rare circumstances where exposure of the adult patient to streptococcal infection is unlikely.

B. Prophylactic Methods

1. Oral

Oral medication depends on patient cooperation. In most instances failures of sulfonamide or penicillin prophylaxis occur in patients who fail to ingest the drug regularly. This can be avoided by long-acting depot penicillin given intramuscularly once a month.

a. *Sulfadiazine*

This drug has the advantage of being easy to administer, inexpensive and effective (other newer sulfonamides are probably as effective). Although resistant streptococci have appeared during mass prophylaxis in the armed forces, this is rare in civilian populations.

(1) Dosage—from 0.5 to 1.0 Gm. taken each morning throughout the year. The smaller dose is to be used in children under sixty pounds.

(2) Toxic Reactions—infrequent and usually minor. In any patient being given sulfonamides, consider all rashes and sore throats as possible toxic reactions especially if they occur in the first eight weeks. In patients on this prophylactic regimen it is hazardous to treat toxic reactions or intercurrent infections with sulfonamides. The chief toxic reactions are:

(a) Skin eruptions: Morbilliform—continue drug with caution. Urticaria or scarlatiniform rash associated with sore throat or fever—discontinue drug.

(b) Leukopenia: Discontinue if white blood count falls below 4,000 and polynuclear neutrophiles below 35 per cent because of possible agranulocytosis which is often associated with sore throat and a rash. Because of these reactions, weekly white blood counts are advisable for the first two months of prophylaxis. The occurrence of agranulocytosis after eight weeks of continuous prophylaxis with sulfonamides is extremely rare.

b. *Penicillin*

Penicillin has the desirable characteristics of being bactericidal for hemolytic streptococci and of rarely producing serious toxic reactions. A careful history of allergic reactions and previous response to penicillin should be obtained.

(1) Dosage—200,000 to 250,000 units once a day, before breakfast.

(2) Toxic reactions:

(a) Urticaria and angioneurotic edema

(b) Reactions similar to serum sickness—includes fever and joint pains and may be mistaken for rheumatic fever.

Although many individuals who have had reactions to penicillin may subsequently be able to tolerate the drug, it is safer not to use penicillin

if the reaction has been severe and particularly if angioneurotic edema has occurred.

Intramuscular benzathine penicillin G

a. Dosage—1,200,000 units once a month.

b. Toxic reactions—same types as with oral penicillin but occur more frequently and tend to be more severe. Some local discomfort usually experienced.

III. Protection of Rheumatic Fever Patients in Hospital Wards

Patients with rheumatic fever or rheumatic heart disease are often exposed to increased hazards in hospital wards as the result of contact with streptococcal carriers or patients with active streptococcal infections. Protection of the rheumatic patient is imperative because of the high rate of recurrence of rheumatic fever following streptococcal infection. In addition to the customary precautions employed to prevent cross infections, the following procedures are recommended:

A. All hospital patients with streptococcal infections should be fully treated by one of the schedules outlined in I-C in order to eliminate streptococci and avoid the carrier state.

B. Patients admitted with acute rheumatic fever should immediately receive a full course of antibiotic therapy (See I-C), whether or not streptococci are isolated from the throat. As soon as the therapeutic course is completed, continuous streptococcal prophylaxis should be instituted (See II, Prevention of Streptococcal Infections).

C. Patients with inactive rheumatic fever or rheumatic heart disease should be placed on continuous streptococcal prophylaxis (See II) on admission to the hospital or as soon thereafter as the diagnosis is established.

IV. Prophylaxis Against Bacterial Endocarditis

In individuals who have rheumatic or congenital heart disease, bacteria may lodge on the heart valves or other parts of the endocardium, producing bacterial endocarditis. Transient bacteremia which may lead to bacterial endocarditis is known to occur following various operative procedures including dental extractions and other dental manipulations which disturb the gums, the removal of tonsils and adenoids, the delivery of pregnant women, and operations on the gastrointestinal or urinary tracts. It is good medical and dental practice to protect patients with rheumatic or congenital heart disease by prophylactic measures.

Recommended Prophylactic Methods

A. *Penicillin* is the drug of choice for administration to patients with rheumatic or congenital heart disease undergoing dental manipulations, or operative procedures in the oral cavity. Although the exact dosage and duration of therapy are somewhat empirical, there is some evidence that for effective therapeutic prophylaxis reasonably high concentrations of penicillin must be present at the time of the operative procedure. The dosage regimens employed for long-term prophylaxis of rheumatic fever are inadequate for this purpose. There is reason to believe that continuous maintenance of penicillin in the blood over a period of several days will result in the death of those organisms which have lodged in the heart valve during the period of transient bacteremia. Not only should penicillin prophylaxis be designed to afford maximum protection, but the method must also be practical. In general, the parenteral route of administration is preferred. All patients should be instructed to report to their physician or clinic should they develop a fever within a month following the operation.

Dosage—600,000 units of aqueous penicillin and 600,000 units of procaine penicillin in oil containing 2 per cent aluminum monostearate administered intramuscularly 30 minutes before the operative procedure.

As an alternative, although considered less desirable, penicillin may be administered by the oral route in dosages of 250,000 to 500,000 units one-half hour before each meal and at bedtime, beginning twenty-four hours prior to the operation and continuing for five days. At the time of the operative procedure it is advisable to give an additional 250,000 units.

Contraindications—Patients who give a history of sensitivity to penicillin.

B. *Other antibiotics*—The broad spectrum antibiotics should be employed as prophylaxis in patients who are sensitive to penicillin or in those who are undergoing surgery of the urinary or lower gastrointestinal tract. Oxytetracycline, chlortetracycline, or erythromycin should be administered in full dosage for five days, beginning treatment the day prior to the surgical procedure.

Committee on Prevention of Rheumatic Fever and Bacterial Endocarditis

T. DUCKETT JONES, M.D., *Chairman**
LEONA BAUMGARTNER, M.D.
MARJORIE T. BELLOWS
BURTIS B. BREESE, M.D.
ANN G. KUTTNER, M.D.
MACLYN MCCARTY, M.D.
CHARLES H. RAMMELKAMP, JR., M.D.

SELECTED REFERENCES

BALDWIN, J. S.: Sulfadiazine prophylaxis in children and adolescents with inactive rheumatic fever. J. Pediat. **30:** 284–288, 1947.

* Died, November 22, 1954.

BREESE, B. B.: Treatment of beta hemolytic streptococcic infections in the home: relative value of available methods. J.A.M.A. **152:** 10–14, 1953.

CHAMOVITZ, R., AND OTHERS: Prevention of rheumatic fever by treatment of previous streptococcal infections. I. Evaluation of benzathine penicillin G., New England J. Med. **251:** 466–471, 1954.

COBURN, A. F., AND MOORE, L. V.: The prophylactic use of sulfanilamide in streptococcal respiratory infections, with especial reference to rheumatic fever. J. Clin. Invest., **18:** 147–155, 1939.

HOUSER, H. B., AND ECKHARDT, G. C.: Recent developments in the prevention of rheumatic fever. Ann. Int. Med. **37:** 1035–1043, 1952.

KUTTNER, A. G., AND REYERSBACH, G.: The prevention of streptococcal upper respiratory infections and rheumatic recurrences in rheumatic children by the prophylactic use of sulfanilamide. J. Clin. Invest. 22: 77–85 (Jan.) 1943.

MASSELL, B. F., AND OTHERS: Prevention of rheumatic fever by prompt penicillin therapy of hemolytic streptococcic respiratory infections: progress report. J.A.M.A., **146:** 1469–1474, 1951.

STOLLERMAN, G. H., AND RUSOFF, J. H.: Prophylaxis against group A streptococcal infections in rheumatic fever patients: use of new repository penicillin preparation. J.A.M.A. **150:** 1571–1575, 1952.

THOMAS, C. B.; FRANCE, R., AND REICHSMAN, F.: Prophylactic use of sulfanilamide in patients susceptible to rheumatic fever. J.A.M.A. **116:** 551–560, 1941.

WANNAMAKER, L. W., AND OTHERS: The effect of penicillin prophylaxis on streptococcal disease rates and the carrier state. New England J. Med. **249:** 1–7, 1953.

FORUM TO 'FORECAST' AMERICA'S HEALTH

A forum on the theme, *Forecasting America's Health* will be sponsored by the American Heart Association along with other member agencies of the National Health Conference at the Hotel Sheraton Astor in New York City March 23 and 24. The forum will discuss economic trends, medical developments and current government progress, and will seek to gauge "how atomic developments will affect health." It will be a feature of Community Health Week, March 21–27, a nationwide observance sponsored by the Junior Chamber of Commerce in cooperation with the National Health Council.

know your diuretic

will your cardiac patients be able to continue the diuretic you prescribe

?

uninterrupted therapy is the key factor in diuretic control of congestive failure. You can prescribe NEOHYDRIN *every day, seven days a week, as needed.*

TABLET

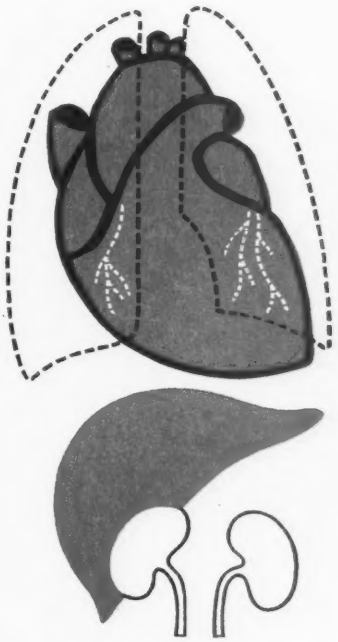
NEOHYDRIN®

BRAND OF CHLORMERODRIN

(18.3 MG. OF 3-CHLOROMERCURI-2-METHOXY-PROPYLUREA IN EACH TABLET)

no "rest" periods... no refractoriness
acts only in kidney...
no unwanted enzyme inhibition
in other parts of the body.

standard for initial control of severe failure MERCUHYDRIN® SODIUM
BRAND OF MERALLURIDE INJECTION



Leadership in diuretic research
Lakeside LABORATORIES, INC., MILWAUKEE 1, WISCONSIN

Circulation

FEBRUARY 1955
VOL. XI NO. 2

The JOURNAL of the AMERICAN HEART ASSOCIATION

CONTENTS

THE CIRCULATORY EFFECTS OF RESERPINE
E. G. McQueen, A. E. Doyle, and F. H. Smirk 161

TREATMENT OF HYPERTENSION WITH RESERPINE, WITH RESERPINE IN COMBINATION WITH PENTAPYRROLIDINIUM, AND WITH RESERPINE IN COMBINATION WITH VERATRUM ALKALOIDS...*A. E. Doyle, E. G. McQueen, and F. H. Smirk* 170

COMBINED RAUWOLFIA-HYDRALAZINE THERAPY OF HYPERTENSIVE PATIENTS
Charles F. Naegele, Ray H. Rosenman, Charles L. Hoffman, and Meyer Friedman 182

CARDIOVASCULAR ACTIONS OF SODIUM NITROPRUSSIDE IN ANIMALS AND HYPERTENSIVE PATIENTS
Irvine H. Page, A. C. Corcoran, H. P. Dustan and Theodore Koppanyi 188

EXPERIMENTAL BACTERIAL ENDOCARDITIS DUE TO STREPTOCOCCUS MITIS. I. METHOD OF INDUCTION.
Robert A. Rabens, Joseph E. Geraci, John H. Grindlay, and Alfred G. Karlson 199

EXPERIMENTAL BACTERIAL ENDOCARDITIS DUE TO STREPTOCOCCUS MITIS. II. PATHOLOGY OF VALVULAR AND SECONDARY LESIONS
Robert A. Rabens, Alfred G. Karlson, Joseph E. Geraci, and Jesse E. Edwards 206

RIGHT VENTRICULAR HYPERTROPHY I. CORRELATION OF ISOLATED RIGHT VENTRICULAR HYPERTROPHY AT AUTOPSY WITH THE ELECTROCARDIOGRAPHIC FINDINGS.....*Isom C. Walker, Jr., Robert A. Helm, and Ralph C. Scott* 215

RIGHT VENTRICULAR HYPERTROPHY II. CORRELATION OF ELECTROCARDIOGRAPHIC RIGHT VENTRICULAR HYPERTROPHY WITH THE ANATOMIC FINDINGS
Isom C. Walker, Jr., Ralph C. Scott, and Robert A. Helm 223

SOME OBSERVATION ON THE RELATION OF THE HIGH-FREQUENCY BED BALLISTOCARDIOGRAM TO THAT OBTAINED FROM AN APERIODIC BED
Dennis C. Deuchar, Samuel A. Talbot, and W. R. Scarborough 228

THE EFFECT OF VENTRICULAR SYSTOLE ON AURICULAR RHYTHM IN AURICULOVENTRICULAR BLOCK .....*Mauricio B. Rosenbaum, and Eugene Lepeschkin* 240

REFLEX VENOMOTOR ACTIVITY IN NORMAL PERSONS AND IN PATIENTS WITH POSTURAL HYPOTENSION
E. B. Page, J. B. Hickam, H. O. Sieker, H. D. McIntosh, and W. W. Pryor 262

THE EFFECTS OF INTRAVENOUS HEXAMETHONIUM ON VENOUS PRESSURE OF NORMOTENSIVE AND HYPERTENSIVE PATIENTS WITH AND WITHOUT CONGESTIVE HEART FAILURE.....*Robert R. Burch* 271

FLOW THROUGH COLLAPSIBLE TUBES: AUGMENTED FLOW PRODUCED BY RESISTANCE AT THE OUTLET.....*Simon Rodbard* 280

CLINICAL PROGRESS. EFFECTS OF VITAMIN DEFICIENCY ON THE HEART AND CIRCULATION.....*M. A. Blankenhorn* 288

Abstracts..... 292

American Heart Association..... 317
(*Including a Statement by the Committee on Prevention of Rheumatice Fever and Bacterial Endocarditis*)